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NEWER METHODS
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TRANSLATED AND REVISED
FROM THE GERMAN

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PUBLISHER'S NOTE

Beginning in 1940, *Die Chemie* published a series of articles on newer methods of preparative organic chemistry. A collection of the articles in book form appeared in 1942, and a second (unrevised) edition in 1944. The present volume was prepared from a photostatic copy of this edition. It contains translations of thirteen of the seventeen articles of the German book, and, in addition, a translation of the article by Wiechert which appeared in *Die Chemie* in 1943.

The German texts were revised in order to eliminate errors, and additions were made to bring the presentation of the various fields up to date. Statements of purely political significance were eliminated. The reader will also find that references to *Chemical Abstracts* have been made instead of, or in addition to, references to *Chemisches Zentralblatt.* Comprehensive subject and compound indexes have been prepared.

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December, 1947

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Oxidations with Lead Tetraacetate and Periodic Acid

By R. CRIEGEE

Translated and revised by Charles O. Edens, Jr., *and* Bruce Graham

Lead tetraacetate was first isolated in 1851 by Jacquelin.[1] The correct formula was advanced in 1896 by Hutchinson and Pollard,[2] who also provided the first useful method of preparation and investigated the properties of the compound in detail. Additional work was done by Colson,[3] in whose papers the lead salts of other fatty acids than acetic acid are described. A practical application of lead tetraacetate was first shown when Dimroth[4] used it with good results as an oxidizing agent in organic chemistry in place of lead dioxide. Lead tetraacetate has the advantage over the dioxide in that it can easily be prepared in 100% purity and that, therefore, calculated amounts can be employed. Much more important, however, is the solubility of the acetate in many organic solvents (acetic acid, benzene, chloroform, tetrachloroethane, and nitrobenzene), which makes it possible to oxidize in homogeneous solution, thus eliminating the great differences in reaction rate which are caused by variations in the surface structure of the lead dioxide. However, lead tetraacetate is by no means only a soluble substitute for lead dioxide; rather, it is able to bring about many oxidations which with other oxidizing agents are either difficult or impossible.

I. PREPARATION OF LEAD TETRAACETATE

In all methods of preparation the starting material used is red lead, which reacts with acetic acid according to the equation

$$Pb_3O_4 + 8\,CH_3COOH \longrightarrow Pb(OCOCH_3)_4 + 2\,Pb(OCOCH_3)_2 + 4\,H_2O \qquad (1)$$

Only one-third of the lead present is thus utilized. It would be better to start with lead dioxide, but this dissolves sufficiently in acetic acid only if it is freshly precipitated. A way for a better utilization of the lead was suggested by Colson.[3] He treated the mother liquor from lead tetraacetate with chlorine, converting one-half of the lead diacetate into lead tetraacetate and the other half into $PbCl_2$.

---

[1] Jacquelin, *J. prakt. Chem.*, **53**, 151 (1851).

[2] Hutchinson and Pollard, *J. Chem. Soc.*, **69**, 212 (1896).

[3] Colson, *Compt. rend.*, **136**, 575, 1664 (1903).

[4] Dimroth, Friedemann, and Kammerer, *Ber.*, **53**, 454 (1920). Dimroth and Hilcken, *ibid.*, **54**, 3050 (1921).

$$2\,Pb(OCOCH_3)_2 + Cl_2 \longrightarrow Pb(OCOCH_3)_4 + PbCl_2 \qquad (2)$$

Oesper and Deasy[5] introduced red lead with simultaneous addition of chlorine into acetic acid–anhydride mixture. The lead chloride can be separated, owing to its lower solubility in hot acetic acid, but the lead tetraacetate must be recrystallized several times to yield an entirely chlorine-free product. If lead chloride is present, the oxidation product may become chlorinated, particularly if one deals with unsaturated compounds.

According to Equation 1, water is formed which hydrolyzes the lead tetraacetate at higher temperatures. The latter should therefore not be allowed to rise above 60°C., particularly toward the end of the reaction. In order to carry out the reaction at a higher temperature and speed up the preparation, it has been suggested that acetic anhydride be added to the acetic acid for combination with the water.[6,7] However, the anhydride, in contrast to the acetic acid, is not entirely stable to oxidation and the yield diminishes. Therefore, the best preparation is that worked out by Dimroth and Schweizer,[8] in which red lead is added through a sieve into commercial acetic acid at 55° to 65°C., with vigorous mechanical stirring. For the preparation of larger quantities this method[9] was somewhat modified.[10]

II. REACTIONS OF LEAD TETRAACETATE

Here only the oxidizing reactions of lead tetraacetate will be discussed. However, it should be pointed out that lead tetraacetate may be used to determine the water content of the non-acid solvents, especially the alcohols.[11] Furthermore, it can esterify alcohols under certain conditions,[9,12] and finally it has found application in sugar chemistry for the substitution of halogens by the acetoxy group.[13] When acting as an oxidizing agent, lead tetraacetate loses two acetoxy groups. Either these can add to a C—C bond or they can substitute hydrogen atoms with esterified OH— groups, or they can combine with two hydrogen atoms during dehydrogenation. This dehydrogenation can take place while the carbon chain is kept intact, or with simultaneous rupture of a carbon to carbon bond.

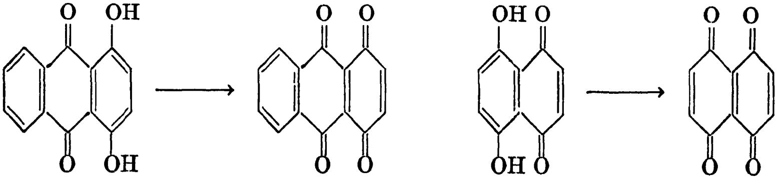
---

[5] Oesper and Deasy, *J. Am. Chem. Soc.*, **61**, 972 (1939).
[6] Hellmuth, Dissertation, Würzburg, 1930.
[7] Clenahan and Hocket, *J. Am. Chem. Soc.*, **60**, 2061 (1938).
[8] Dimroth and Schweizer, *Ber.*, **56**, 1375 (1923).
[9] Criegee, *Ann.*, **481**, 236 (1930).
[10] Mendel, *Rec. trav. chim.*, **59**, 720 (1940).
[11] Criegee, Kraft, and Rank, *Ann.*, **507**, 159 (1933).
[12] Montignie, *Bull. soc. chim.*, **1**, 1280 (1934).
[13] Ohle and Marececk, *Ber.*, **63**, 612 (1930).

In all cases the lead diacetate which is formed during oxidation is easily soluble in acetic acid but it precipitates from benzene, chloroform, etc. The separation of the reaction products from these solvents is therefore simple. The acetic acid solution can be poured into water, whereby the reaction products not soluble in water will separate. In the case of water-soluble products, lead can be separated in the usual way. Possible excess lead tetraacetate can be destroyed by adding oxalic acid or glycol to the reaction mixture.

III. DEHYDROGENATION WITH LEAD TETRAACETATE

Because of its high, though not exactly measured, oxidation potential, lead tetraacetate can, according to Dimroth,[4] convert all known oxidation-reduction systems into their oxidized state. Thus all of the hydroquinones can be oxidized to quinones and all the leuco dyes can be oxidized to dyes. The rare di- and triquinones (the latter only in solution) of the anthraquinone and naphthoquinone series[14] can be produced by this oxidation.

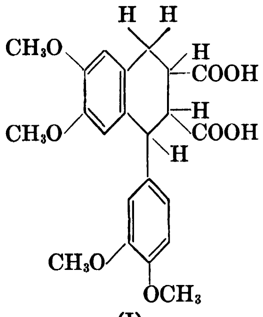


Also, according to Heller,[15] indigo is smoothly changed into dehydroindigo. All of the above oxidations can be carried out in acetic acid or benzene at room temperature. However, a final heating may be advisable because of the low solubility of the starting materials. The yield is quantitative.

The dehydrogenation of hydroaromatic compounds proceeds less smoothly. Δ^2-Dihydronaphthalene, nevertheless, gives a 70% yield of naphthalene. However, with the Δ^1 isomer, a different reaction takes place. Tetralin as well as cyclohexene and cyclohexadiene are not converted, even in traces, into naphthalene and benzene, respectively.[9] On the other hand, Erdtman[16] discovered that the tetralin derivative (I) substituted with methoxy and carboxy groups is comparatively smoothly dehydrogenated into a naphthalene derivative. The yield from the 9,10-dihydroanthracene de-

---

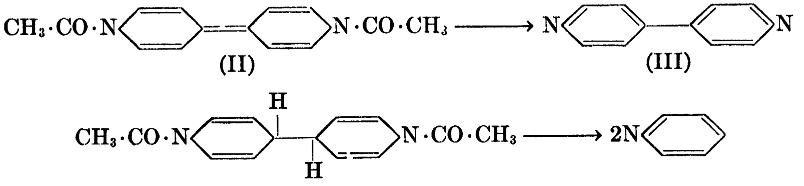
[14] Zahn and Ochwat, *Ann.*, **462**, 72 (1928).
[15] Heller, *Ber.*, **69**, 563 (1934).
[16] Erdtman, *Ann.*, **513**, 229 (1934).



(I)

hydrogenation, which proceeds in a benzene solution at 70°C, is only 25%, since the anthracene itself is attacked.

Dehydrogenations in the heterocyclic series seem to proceed more readily according to Hahn.[17] Yohimbine gives 50 to 60% yields of tetradehydroyohimbine. Schöpf[18] found that lead tetraacetate is very useful for the dehydrogenation of complicated dihydropyrimidine derivatives. The diacetyl dihydro-γ,γ-dipyridyl (II), according to Dimroth,[19] undergoes deacetylation into γ,γ-dipyridyl (III), while the corresponding tetrahydro compound (IV) suffers cleavage under the same conditions and gives pyridine.



(II) (III)

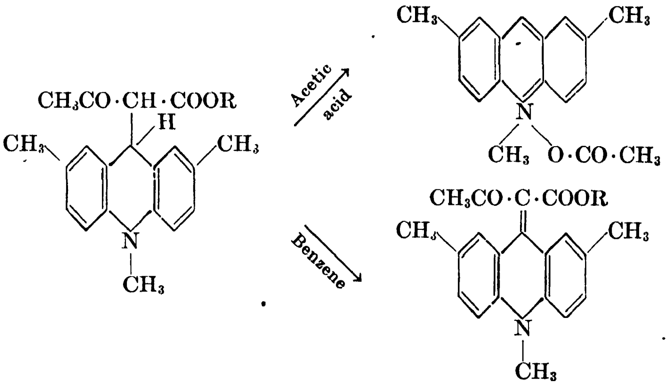
(IV)

A similar cleavage occurs when the dihydroacridine derivative (V) is treated in acetic acid solution with lead tetraacetate, while the dehydrogenation to VI occurs in a benzene solution, without cleavage.[20] Benzaldehyde-imine hydrochloride, $C_6H_5CH{:}NH \cdot HCl$, is converted smoothly into benzonitrile, C_6H_5CN. The reaction in acetic acid solution produces heat and must be cooled externally.[21]

The dehydrogenation of alcohols to aldehydes and ketones represents a special type of reaction. It does not occur in acetic acid, but only in benzene solution. The presence of pyridine for combining with the acetic acid

[17] Hahn, Kappes, and Ludwig, *Ber.*, **67**, 686 (1934).
[18] Schöpf and Oechster, *Ann.*, **523**, 1 (1936).
[19] Dimroth and Frister, *Ber.*, **55**, 1223 (1922).
[20] Criegee, Dissertation, Würzburg, 1925.
[21] Bollinger, Dissertation, Marburg, 1936.

liberated seems to favor the reaction. Thus, these alcohols, benzyl alcohol, cinnamic alcohol, geraniol, and fluorenol, give fair yields of benzaldehyde, cinnamic aldehyde, citral, and fluorenone,[22] respectively. An extension of



(V) (VI)

this method appears worth while and promising. However, the speed of the reaction is many times smaller than that of the oxidative cleavage of glycols and there is no harmful side reaction in the splitting of the glycols.

IV. SUBSTITUTION OF H— BY —OCOCH$_3$

A direct substitution of a hydrogen atom by an OH group is practical only in rare cases. With lead tetraacetate it is frequently feasible because the hydroxyl group is acetylated and is thus protected against further oxidation. However, the hydrogen atom which is to be replaced must be activated by the neighboring substituents. Therefore, paraffins do not react with lead tetraacetate, while a substitution in the aromatic nucleus is usually possible. Benzene itself is stable toward the oxidizing agent, but naphthalene is slowly attacked and anthracene yields the same products as it does when treated with lead dioxide and acetic acid,[23] namely, 9-anthrol acetate and 10-hydroxyanthrone acetate.

The reaction proceeds much better with more highly condensed ring systems, according to Fieser.[24] Thus, 1,2-benzanthracene (VII) at 100°C. in acetic acid is substituted in the 10 position, giving a 52% yield of 1,2-benz-10-anthranyl acetate. 1,2,5,6-Dibenzanthracene (VIII) is stable toward lead tetraacetate (perhaps owing to steric hindrance) and can be purified from the more readily oxidizable chrysene (IX). The 3,4-benzo-

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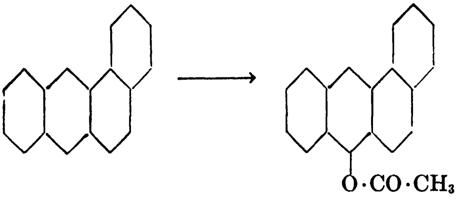
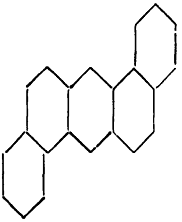
[22] Criegee, unpublished.

[23] Meyer, *Ann.*, **379**, 67 (1911).

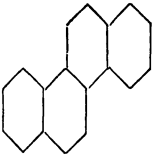
[24] Fieser and Hershberg, *J. Am. Chem. Soc.*, **60**, 1893 (1938); **61**, 1565 (1939).



(VII)

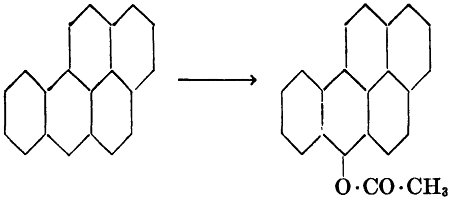


(VIII)



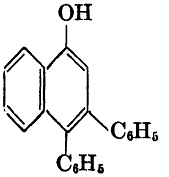
(IX)

pyrene (X) and its derivatives react even better. In a benzene solution at 20°C. the reaction is completed in $^1/_2$ hour with an 85% yield of XI. It is remarkable that the affinities of aromatic hydrocarbons for oxidation by lead tetraacetate parallel their carcinogenic activities.

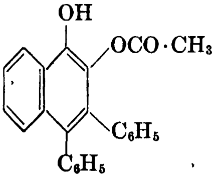


(X) (XI)

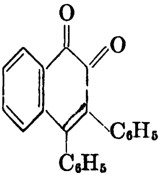
Smith and Hoehn[25] have shown that under certain circumstances the substitution in the nucleus is influenced by substituents already present. Thus, the naphthalene derivative (XII) is changed to XIV, a naphthoquinone derivative, presumably by way of XIII. A systematic investigation of the influence of substituents is not as yet available.



(XII)



(XIII)



(XIV)

The saturated side chains are attacked more easily than the nuclear hydrogen atoms and always in the α position. According to Dimroth,[8] toluene, diphenyl-, and triphenylmethane are changed with increasing ease to the acetates of benzyl alcohol, benzohydrol, and triphenylcarbinol, respectively. In the first two cases the yields amount to 20 and 35%, respectively, and the reactions take place only in the presence of heat. Likewise, tetralin (XV) is substituted in the saturated nucleus (XVI).[9] The same is true for acenaphthene (XVII)[22,26] and for methylcholanthrene[27] (XVIII). The latter reacts in benzene–acetic acid solution at 0°C. to give a 46% yield of XIX along with a 7% yield of XX, which is presumably formed by way of the diacetoxy compound. The methyl group in the benzanthracene derivative (XXI) is much less easily oxidized and therefore the yield of XXII is correspondingly smaller.

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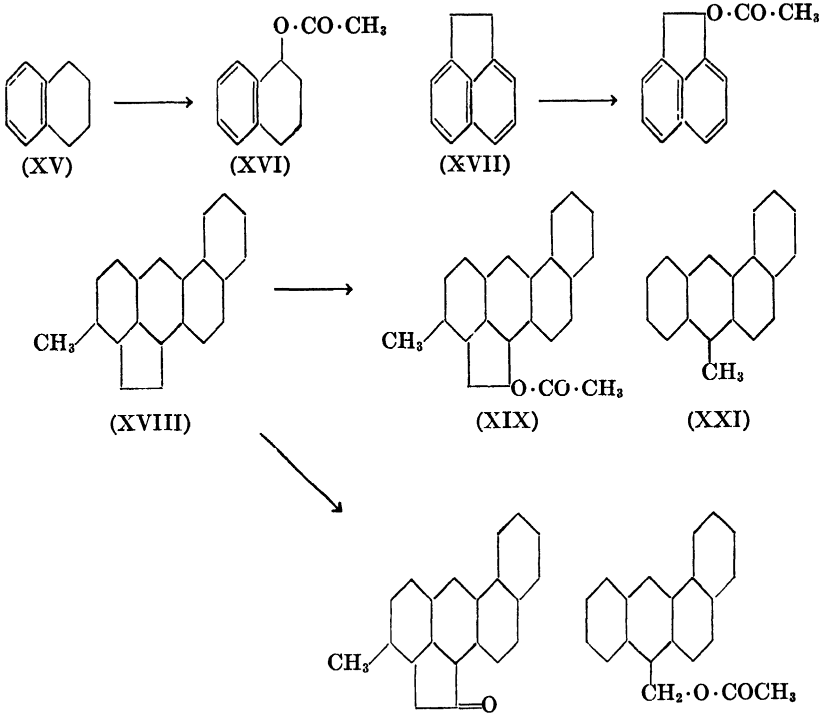
[25] Smith and Hoehn, *J. Am. Chem. Soc.*, **61**, 2619 (1939).



(XV) (XVI) (XVII)

(XVIII) (XIX) (XXI)

(XX) (XXII)

Olefins which have methylene groups next to their double bonds can be substituted at the methylene groups. In these cases addition to the double bond and substitution adjacent to the double bond occur simultaneously. Thus, cyclopentene,[28] cyclohexene,[9] and indene[9] can be converted to the esters of the corresponding unsaturated alcohols, (XXIII), (XXIV), and (XXV), with yields of approximately 20%. Introduction of the OH—group into the various terpenes has been tried in this manner but the results have been less satisfactory.[29] Only camphene (XXVI) reacts

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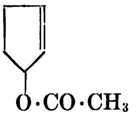
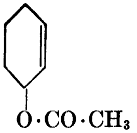
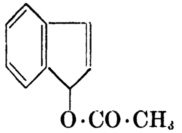
[26] Brown and Yee, *J. Am. Chem. Soc.*, **67**, 874 (1945).
[27] Fieser and Hershberg, *J. Am. Chem. Soc.*, **60**, 2542 (1938).
[28] Dane and Eder, *Ann.*, **539**, 207 (1939).
[29] Ward, *J. Am. Chem. Soc.*, **60**, 325 (1938).



(XXIII)

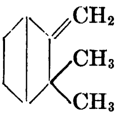


(XXIV)

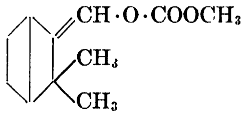


(XXV)

smoothly, according to Hückel,[30] giving a 75% yield of enol acetate of camphenilanaldehyde (XXVII). The reaction of this olefin is unique in that the hydrogen on the double bond carbon is replaced.



(XXVI)



(XXVII)

Ketones, α-keto esters, and dicarboxylic acid esters often undergo substitution even more readily than do the hydrocarbons. Here the hydrogen atom is activated by the adjacent carbonyl or carboxyl group. According to Dimroth,[8] acetone yields the acetic acid esters of hydroxy and dihydroacetone, and acetophenone gives benzoylcarbinol. Although the yields have not been very satisfactory, this method has found use in the changing of a—$COCH_3$ group into a-$COCH_2OH$ group in the sex hormone series.[31,32] The α-keto acid esters react under mild conditions. The α-acetoxyacetoacetic ester, $CH_3COCH(OCOCH_3)COOC_2H_5$, is produced from acetoacetic ester in 40% yield at a temperature of 30°C. Ethyl benzoylacetate forms an analogous reaction product in a 45% yield. Malonic ester is more difficult to oxidize, producing the acetate of tartronic acid ester. Simple fatty acids do not react appreciably with lead tetraacetate, although boiling acetic anhydride is oxidized in both CH_3—groups. CH_3COO—groups enter and the anhydride of the *O*-acetyl glycolic acid is formed. An induced oxidation of the lower fatty acids to the esters of the corresponding α-hydroxy fatty acids takes place under remarkably mild conditions in the course of the oxidation of cyclopentadiene (see below). Nitriles and aliphatic nitro compounds are apparently not attacked.[22] In the heterocyclic series, Siedel[33, 34] used lead tetraacetate for the oxidation of the pyrrole derivative (XXVIII). Here substitution takes place both in the nucleus and in the side chain.

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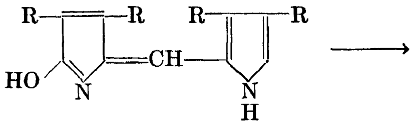
[30] Hückel and Hartmann, *Ber.*, **70**, 959 (1937).

[31] Erhard, Ruschig, and Aumuller, *Ber.*, **72**, 2035 (1939); *Angew. Chem.*, **52**, 363 (1939).

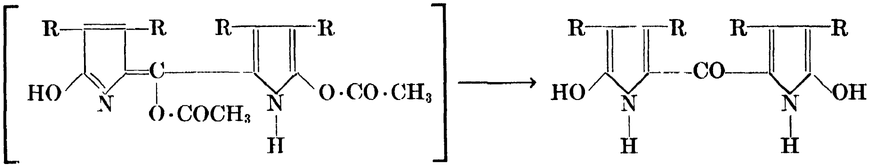
[32] Reichstein and Montigel, *Helv. Chim. Acta*, **22**, 1212 (1939).

[33] Siedel and Moller, *Z. physiol. Chem.*, **259**, 113 (1939).

[34] Seidel and Winkler, *Ann.*, **554**, 162 (1943).

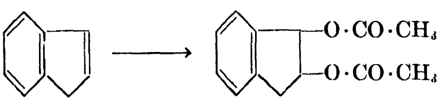


(XXVIII)

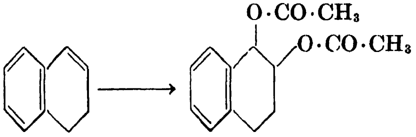


V. ADDITION OF TWO ACETYLATED OH— GROUPS TO DOUBLE BONDS

Simple aliphatic olefins seem as yet not to have been tested for their behavior toward lead tetraacetate. With cycloolefins substitution in the α position and addition to the double bond occur in most cases simultaneously. Generally a mixed *cis* and *trans* addition takes place. However, a systematic stereochemical investigation is still lacking. Cyclopentene when oxidized at 50°C. gives an 18% yield of the diacetate of cyclopentane-1,2-diol.[28] Correspondingly cyclohexene gives a mixture of the cyclohexanediols.[9] The pure *trans*-diols were isolated in the oxidation of indene (XXIX, 18% yield) and of Δ^1-dihydronaphthalene (XXX, 45% yield).



(XXIX)



(XXX)

However, the simultaneous formation of the *cis* compound is entirely possible. When positive substituents, especially the CH_3O— groups, are present in the molecule, the addition is usually easier and proceeds more smoothly. Anethole (XXXI)[8,9] and isoeugenol methyl ether (XXXII)[9] react readily at room temperature in acetic acid solution and produce in good yield mixtures of the stereoisomeric diacetoxy addition products. Fischer obtained from the acetal (XXXIII) in benzene solution at 50°C. an 80% yield of the compound (XXXIV), and from the latter, the dihydroxyacetone.[35] Helferich[36] obtained from the glucoseenide (XXXV) at room temperature and in benzene solution a 60% yield of a derivative of 5-ketoglucose. Zervas,[37] under similar conditions, prepared a fructose derivative from an unsaturated styracitol.

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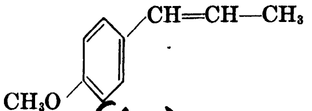
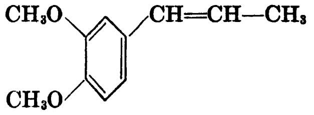
[35] Fischer, Baer, and Feldmann, *Ber.*, **63,** 1732 (1930).

[36] Helferich and Bigelow, *Z. physiol. Chem.*, **200,** 263 (1931).

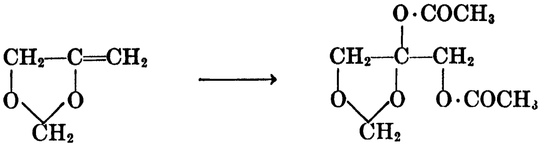
[37] Zervas and Papadimilrin, *Ber.*, **73,** 174 (1940).



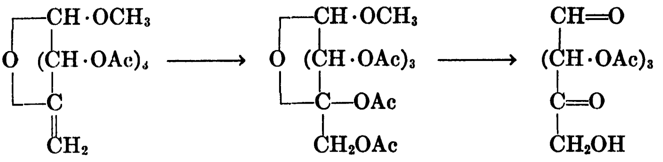
(XXXI)



(XXXII)

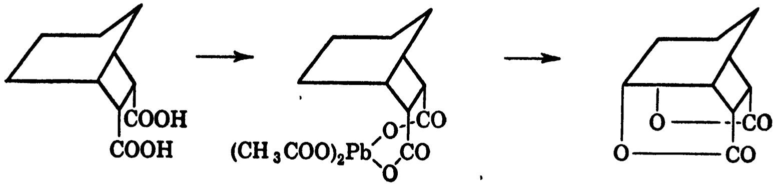


XXXIII) (XXXIV)



(XXXV)

Unsaturated compounds with negative substituents are, on the other hand, much more difficult to attack. Crotonaldehyde, $CH_3CH:CH:O$, starts to react noticeably at 80°C. and yields unsymmetrical reaction products.[22] Especially interesting is the behavior of the acid (XXXVI), which is obtained from cyclopentadiene and maleic anhydride. It does not give the diacetate of a dihydroxydicarboxylic acid, but immediately forms the dilactone (XXXVII). Probably there is an intermediate lead tetra salt of the acid (XXXVI) and the reaction proceeds as an intramolecular addition.



(XXXVI) (XXXVII)

The behavior of compounds with conjugated double bonds has been investigated rather thoroughly.[9] They are attacked much more easily by lead tetraacetate than are simple olefins, the reaction velocity varies greatly with the individual compounds, increasing strongly in the series dimethylbutadiene, cyclohexadiene, and cyclopentadiene (XXXVIII). The first two compounds add the acetate radicals chiefly in the 1,2 position. The addition to the cyclopentadiene proceeds in the 1,2 and in the 3,4 positions, leading to a mixture of the *cis* and *trans* forms in both cases.[38]

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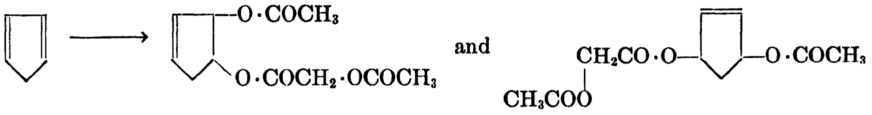
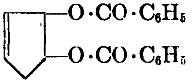
[38] Criegee and Beucker, *Ann.*, **541**, 218 (1939).

The composition of the mixture is affected by the solvent. The oxidation of cyclopentadiene, and to a lesser extent cyclohexadiene and anethole, is complicated by oxidation of acetic acid to glycolic acid. This latter reaction is noteworthy, because it proceeds under conditions under which a direct oxidation of acetic acid or of one of its derivatives to glycolic acid does not take place. The main product of the oxidation is a mixture of esters (XXXIX) and (XL). Analogous reaction products are produced with lead tetrapropionate and lead tetrabutyrate, while lead tetrabenzoate gives a good yield of the normal product (XLI) in its *trans* form.



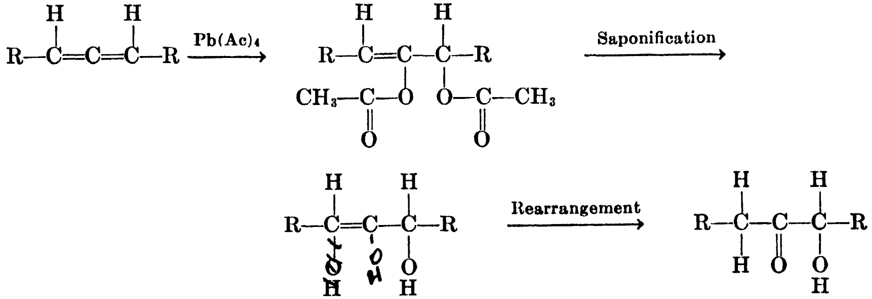
(XXXVIII) (XXXIX) (XL)



(XLI)

Ergosterol-B$_3$-acetate serves as an example of more complicated dienes; it forms the triacetate of an ergostadienetriol.[39-43]

The behavior of lead tetraacetate toward compounds containing cumulated double bonds has been investigated by LaForge and Acree.[44] α-Hydroxy ketones are produced from substituted allenes as shown by the following equation.



This reaction can be used as a method for identifying the cumulated system.

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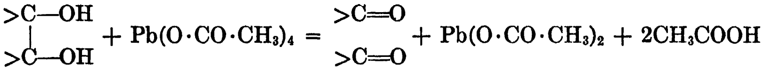
[39] Yun Hwang Chen, *Ber.*, **70**, 1433 (1937).
[40] Christiani and Anger, *Ber.*, **72**, 1124 (1939).
[41] Windaus and Riemann, *Z. physiol. Chem.*, **274**, 206 (1942).
[42] Windaus, *Z. physiol. Chem.*, **276**, 280 (1942).
[43] Windaus, Riemann, Rüggeberg, and Zühlsdorff, *Ann.*, **552**, 142 (1942).
[44] LaForge and Acree, *J. Org. Chem.*, **6**, 208 (1941).

VI. GLYCOL CLEAVAGE BY MEANS OF LEAD TETRAACETATE

One of the most important reactions involving the use of lead tetraacetate is that by which a C chain is split between two hydroxyl-bearing carbon atoms.[45] The reaction proceeds under the mildest conceivable conditions, *i.e.*, in dilute acetic acid or benzene solution at room temperature, to yield aldehydes or ketones. The reaction rate in inert solvents is greater by



$$\begin{array}{l} >\mathrm{C{-}OH} \\ \;\;| \\ >\mathrm{C{-}OH} \end{array} + \mathrm{Pb(O\cdot CO\cdot CH_3)_4} = \begin{array}{l} >\mathrm{C{=}O} \\ \\ >\mathrm{C{=}O} \end{array} + \mathrm{Pb(O\cdot CO\cdot CH_3)_2} + 2\mathrm{CH_3COOH}$$

several orders of magnitude than it is in glacial acetic acid.[11] It is noteworthy that the addition of methanol or water also greatly increases the reaction rate.[46] Recently Baer, Grosheintz, and H. O. L. Fischer carried out preparative glycolic fissions using lead tetraacetate in aqueous media.[47,48] The following discussion will be limited to the synthesis of carbonyl compounds. The mechanics of the reaction[11,49–51] and the numerous analytical applications of the diol cleavage for identification, recognition, quantitative determination, and ascertainment of the configuration of diols, and the analytical degradation of suitable natural products will be omitted. However, mention should be made of the recently discovered use of lead tetraacetate as an alkylating agent, described by Fieser and co-workers.[52,53]

The oxidative splitting of an aliphatic glycol produces simple aldehydes or ketones. Thus, glyoxalic esters which are not easily accessible otherwise can be obtained conveniently from tartaric esters.[54]

$$\mathrm{ROOC{-}CHOH{-}CHOH{-}COOR} \longrightarrow 2\ \mathrm{OCH{-}COOR}$$

Dihydroxystearic acid can serve as a starting material for pelargonic aldehyde and azelaaldehyde acid.[55–57] The splitting of α ethers of glycerol, $\mathrm{RO{-}CH_2{-}CHOH{-}CH_2OH}$, produces the ethers of glycolic aldehydes, $\mathrm{ROCH_2CHO}$, used in perfumes.[58] In many cases one can proceed from olefins by adding two hydroxyl groups to the double bonds by well known methods and oxidizing with lead tetraacetate.

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[45] Criegee, *Ber.*, **64,** 260 (1931).

[46] Criegee and Büchner, *Ber.*, **73,** 563 (1940).

[47] Baer, Grosheintz, and H. O. L. Fischer, *J. Am. Chem. Soc.*, **61,** 2607 (1939).

[48] Grosheintz, *J. Am. Chem. Soc.*, **61,** 3379 (1939).

[49] Criegee, *Sitzber. Ges. Beforder. ges. Naturw. Marburg*, **69,** 25 (1934); *Chem. Zentr.*, **1934, II,** 2515; *Chem. Abstracts*, **29,** 6820 (1935).

[50] Criegee, *Angew. Chem.*, **50,** 153 (1937).

[51] Bell, Sturrock, and Whitehead, *J. Chem. Soc.*, **1940,** 82.

[52] Fieser and Chang, *J. Am. Chem. Soc.*, **64,** 2043 (1942).

[53] Fieser, Clapp, and Daudt, *J. Am. Chem. Soc.*, **64,** 2052 (1942).

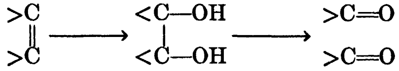
[54] Weygand, *Organic Preparations*, Interscience, New York, 1945, p., 455.

[55] Sabetay, *Bull. soc. chim.*, **2,** 1744 (1935).

[56] Scanlan and Swern, *J. Am. Chem. Soc.*, **62,** 2305 (1940).

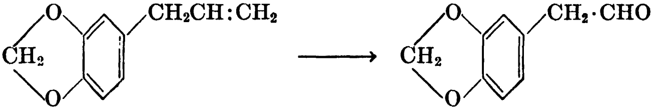
[57] Hilditch and Jasperson, *Nature*, **147,** 327 (1941).

[58] Chi-Yi-Hsing and Kon-jen Chang, *J. Am. Chem. Soc.*, **61,** 3589 (1939).

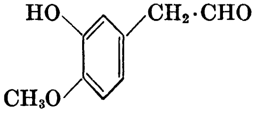


$$\begin{matrix} \gt C & & \lt C\text{—}OH & & \gt C\text{=}O \\ \| & \longrightarrow & | & \longrightarrow & \\ \gt C & & \lt C\text{—}OH & & \gt C\text{=}O \end{matrix}$$

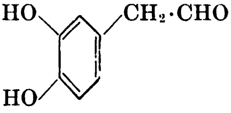
In this way the same oxidative cleavage of a double bond is attained as with ozone, but the yields are usually much better. Erdtmann[59] and Späth[60] thus prepared homopiperonal (XLIII) from safrole (XLII) and Schöpf[61,62] in the same way prepared homoisovanillin (XLIV) and homoprotocatechualdehyde (XLV). Correspondingly Robinson[63] had previously obtained levulinic aldehyde from methylheptenone. Two general methods to obtain rare aldehydes originated with Hershberg[64] and with Grundmann.[65] The former starts with an alkyl halide, R—Br, transforms the Mg compound with allyl chloride into R—CH_2—CH—CH_2, adds two hydroxyl groups to the double bond according to a method devised by Prevost,[66] and then forms the aldehyde, R—CH_2—CHO, by the lead tetraacetate cleavage.[67] Grundmann changed carboxylic acids by means of glycolic cleavage into the corresponding aldehydes, which is not always easily done in a direct way. The reaction proceeded in the following stages.



(XLII) (XLIII)



(XLIV)



(XLV)

$$\text{R·COOH} \longrightarrow \text{R·COCl} \longrightarrow \text{R—CO·CHN}_2 \longrightarrow \text{R—CO·CH}_2\text{·OCOCH}_3$$
$$\longrightarrow \text{R—CH(OH)CH}_2\text{OH} \longrightarrow \text{R—CH=O}$$

Glycolic cleavage is especially useful in the preparation of rare sugars and sugar derivatives. It is advisable to start with materials which possess only two adjacent free hydroxyl groups, since otherwise the reaction becomes more complicated. *d*-Glyceraldehyde, which previously was difficult to obtain, can be prepared easily by the glycolic cleavage. Its dibenzoyl compound is made from tetrabenzoylmannitol[68] while the free sugar, according to H. O. L. Fischer, [48, 69–71] is formed from mannitol by means of its diacetone compound. From the acetal of the glyceraldehyde so obtained

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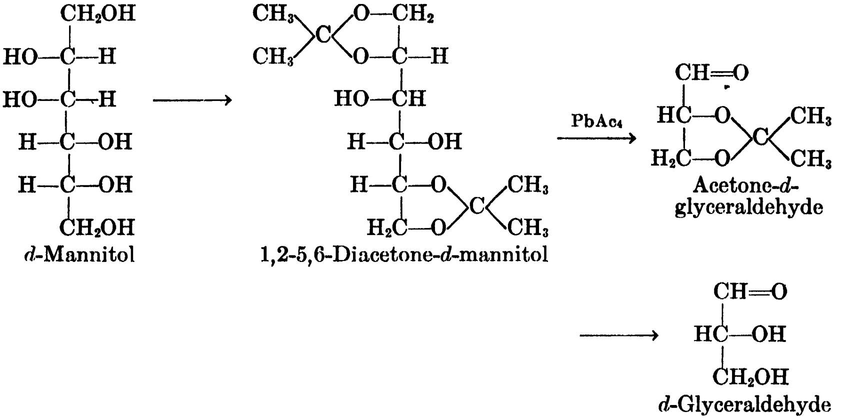
[59] Erdtmann and Robinson, *J. Chem. Soc.*, **1933**, 1530.
[60] Spath, Kuffner, and Kesztler, *Ber.*, **69**, 382 (1936).
[61] Schöph and Salzer, *Ann.*, **544**, 1 (1940).
[62] Schopf and co-workers, *Ann.*, **544**, 30 (1940).
[63] Blount and Robinson, *J. Chem. Soc.*, **1933**, 1511.
[64] Hershberg, *Helv. Chim. Acta*, **17**, 351 (1934).
[65] Grundmann, *Ann.*, **534**, 189 (1936).
[66] Prevost, *Compt. rend.*, **196**, 1129 (1933); **197**, 1661 (1933).
[67] Butenandt and Peters, *Ber.*, **71**, 2688 (1938).



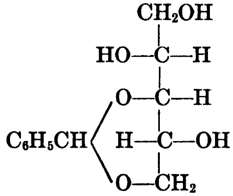
d-Mannitol

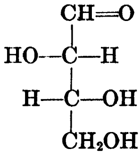
1,2-5,6-Diacetone-*d*-mannitol

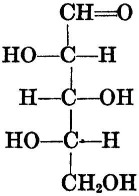
Acetone-*d*-glyceraldehyde

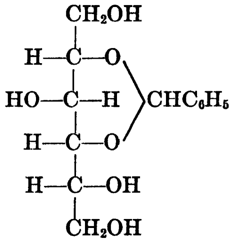
d-Glyceraldehyde

the important synthetic substance, glyoxal hemiacetal, $OCH{=}CH(OC_2H_5)_2$[72] can be prepared through a second cleavage. Steiger and Reichstein[73] obtained *d*-threose (XLVII), a representative of the rare C_4-sugars, by the oxidation of benzalarabitol (XLVI). *l*-Xylose (XLVIII) can be prepared from 2,3-benzalsorbitol[74–76] (XLIX) or from diethylidenesorbitol.[77] A derivative of *d*-arabinose can be obtained from 2,4-ditosylmannitol.[78]


(XLVI)


(XLVII)


(XLVIII)


(XLIX)

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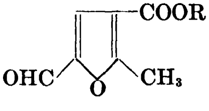
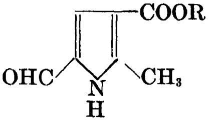
[68] Brigl and Grüner, *Ber.*, **66**, 931 (1933).
[69] H. O. L. Fischer and Baer, *Helv. Chim. Acta*, **17**, 622 (1934).
[70] Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 463 (1939).
[71] Baer and H. O. L. Fischer, *J. Am. Chem. Soc.*, **61**, 761 (1939).
[72] H. O. L. Fischer, *Helv. Chim. Acta*, **18**, 514 (1935).
[73] Steiger and Reichstein, *Helv. Chim. Acta*, **19**, 1016 (1936).
[74] Vargha, *Ber.*, **68**, 18 (1935).
[75] Vargha, *Ber.*, **68**, 1377 (1935).
[76] Micheel and Hasse, *Ber.*, **68**, 1582 (1935).
[77] Appel, *J. Chem. Soc.*, **1935**, 425.
[78] Müller, *Ber.*, **67**, 830 (1934).

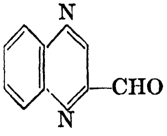
Certain heterocyclic aldehydes (L, LI, LII)[79] result from the condensation products of sugars or amino sugars with acetoacetic ester and *o*-phenylenediamine. Here, similarly as Kuhn had already observed with lactoflavin,[80,81] the whole saccharoid side chain, —$(CHOH)_3CH_2OH$, is split off and changed into an aldehyde group.



(L)



(LI)



(LII)

If cyclic glycols are oxidized with lead tetraacetate, a dialdehyde, a diketone, or a ketoaldehyde is produced instead of two segments. It is of special significance that the dialdehydes which are otherwise difficult to obtain can be produced by this means, although the yields are variable because of the instability of these compounds. Glutar- and adipodialdehyde result from the splitting of cyclopentanediol[82] and cyclohexanediol.[45,83] 1,2-Dihydroxytetralin yields the dialdehyde (LIII)[84] hydrindenediol produces the homophthaldialdehyde (LIV),[85] and camphor glycol, the dialdehyde (LV).[86] The naphthaldialdehyde (LVI) in the hydrate form can be obtained from acenaphthenediol,[11,87] while Alder[88] produced the dilactone of the hydrate form of the dialdehyde (LVII) from the corresponding dihydroxy compound. In other cases, as in the oxidation of quinic acid methyl ester,[47] certain glycosides,[48] and for the synthesis of auxinglutaric acid,[89] the intermediate dialdehydes were not isolated but were changed immediately into dicarboxylic acids.

Cyclic ditertiary glycols are readily oxidized to diketones. This reaction can be accomplished with many other oxidizing agents, but lead tetraacetate produces by far the best results, especially if other oxidizable groups are present in the molecule. *peri*-Diacetylnaphthalene (LVIII) was thus obtained from an acenaphthene derivative[11]; the corresponding dibenzoyl compound as well as dibenzoyldiphenyl are likewise easily obtainable. Kuhn[90] oxidized strongly unsaturated carotene glycol to the un-

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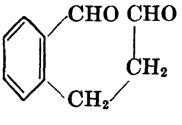
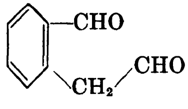
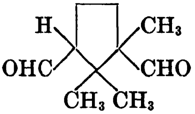
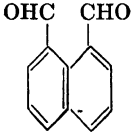
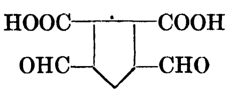
[79] Müller and Vargha, *Ber.*, **72,** 1993 (1939).
[80] Kuhn, Rudy, and Wagner-Jauregg, *Ber.*, **66,** 1950 (1933).
[81] Kuhn, Rudy, and Weygand, *Ber.*, **68,** 625 (1935).
[82] Schöpf and Lehmann, *Ann.*, **518,** 1 (1935).
[83] Kennedy and Robinson, *J. Chem. Soc.*, **1932,** 1429.
[84] Blount, *J. Chem. Soc.*, **1933,** 553.
[85] Blount and Robinson, *J. Chem. Soc.*, **1933,** 955.
[86] Häflinger, *Helv. Chim. Acta*, **23,** 90 (1940).
[87] Blount and Weissberger, *J. Chem. Soc.*, **1936,** 336.
[88] Alder and Schneider, *Ann.*, **524,** 189 (1936).
[89] Kögl and Erxleben, *Z. physiol. Chem.*, **235,** 181 (1935).
[90] Kuhn and Brockmann, *Ann.*, **516,** 95 (1935).

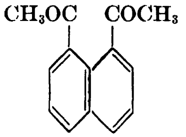

(LIII)

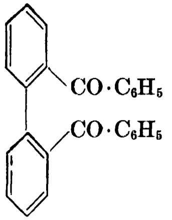

(LIV)


(LV)


(LVI)


(LVII)


(LVIII)


(LIX)

saturated diketone, without oxidizing the double bonds. A polycyclic ketoaldehyde results in crystalline form from the oxidation of an ergostadienetriol.[91]

· The oxidative fission is not limited to α-glycols. The α-hydroxy acids react just as smoothly according to the equation, R—CHOH—COOH → R—CHO + CO_2, forming aldehydes or ketones and carbon dioxide.[11,92-95] An especially useful reaction of this type is the degradation of carboxylic acids, R—CH_2—COOH, through the stages, R—CHBr—COOH, R—CHOH—COOH, and R—CHO to R—COOH. The previously used method of changing the hydroxy acid by way of its ester into a tertiary glycol, R—CHOH—$C(CH_3)_2OH$, and then subjecting this to oxidation by lead tetraacetate is superfluous. The degradation was first applied by Karrer[96] and by Raudnitz[97] to perhydrocrocetin and perhydronorbixin and was later used by Kögl[98] for determining the constitution of the auxin-glutaric acids. The reaction was thoroughly studied by Mendel and Coops[99] from a preparative point of view.

The fission of α-hydroxyketones and α-hydroxyaldehydes does not proceed so well. Reichstein[100] used it for the degradation of sterol derivatives of the formulas R—CO—CHOH—CH_2OH and R—CHOH—CO—CH_2OH. These were changed to R—COOH and R—CHO.[101]

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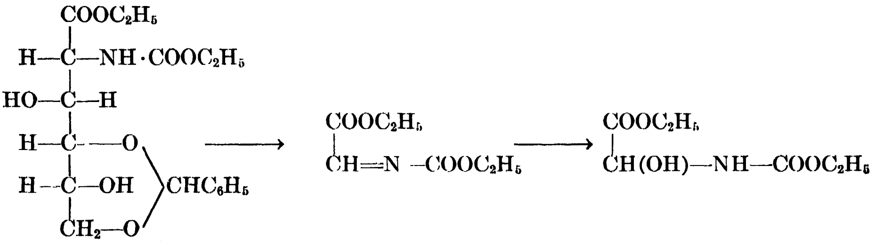
[91] Huang Minlon, *Ber.*, **72,** 854 (1939).
[92] Oêda, *Bull. Chem. Soc. Japan*, **9,** 8 (1934); *C. A.*, **28,** 2700 (1934).
[93] H. O. L. Fischer, *Ber.*, **65,** 1009 (1932).
[94] Knoop and Mitarbeiter, *Z. physiol. Chem.*, **239,** 30 (1936).
[95] Klenk and Clarenz, *Z. physiol. Chem.*, **257,** 268 (1939).
[96] Karrer, *Helv. Chim. Acta*, **15,** 1399 (1932).
[97] Raudnitz and Perchel, *Ber.*, **66,** 901 (1933).
[98] Kögl and Erxleben, *Z. physiol. Chem.*, **227,** 51 (1934).
[99] Mendel and Coops, *Rec. trav. chim.*, **58,** 1133 (1939).
[100] Reichstein, *Helv. Chim. Acta*, **19,** 1114 (1936).
[101] See also for the oxidation of α-keto acids the work of Baer, *J. Am. Chem. Soc.*, **62,** 1597 (1940).

More important, but still little investigated, is the application of glycolic fission to nitrogenous substances. An —NH_2 or —NH group is equivalent to an —OH group in rendering a compound oxidizable by lead tetraacetate. Thus α-diamines, α-amino alcohols, and α-amino acids can be oxidized with lead tetraacetate.[21,102] However, the expected imines, R—CH=NH, usually undergo dehydrogenation to produce nitriles, RCN. Thus phenylglycine, $C_6H_5CH(NH_2)$—COOH, produces benzonitrile in a smooth reaction. If the H atom on the nitrogen is protected, by a tosyl group for example, the reaction stops at the stage of the imine, R—CH=NTsl. In contrast to the tosyl derivatives, the acetyl and benzoyl compounds of the amino acids and diamines are not attacked at all, possibly because they react exclusively in a tautomeric form. On the basis of this fact, Knoop[94] could distinguish serine, CH_2OH—$CH(NH_2)$—COOH, and isoserine, $CH_2(NH_2)$—CH(OH)—COOH. Only the latter's *N*-benzoyl compound reacts with lead tetraacetate. The ability to protect the amino group does not extend to the carbethoxy residue, for Karrer[103] effected the oxidation of the glucosamine derivative (LX) by 8 hours of refluxing in benzene solution.



(LX)

VII. OXIDATIONS WITH PERIODIC ACID

The ability of periodic acid, H_5IO_6—$HIO_4 \cdot 2H_2O$, to oxidize organic compounds in a lucid reaction was discovered in 1928 by Malaprade,[104] when he was looking for a quantitative method to determine iodic acid and periodic acid in each other's presence. In the following years particularly, Fleury and his co-workers investigated its applications to organic materials; through his works [105–107] periodic acid became commonly known to organic chemists. Its reactions correspond to those of lead tetraacetate and it functions just as quantitatively and easily in the glycol cleavage.

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[102] Leonard and Rebenstorf, *J. Am. Chem. Soc.*, **67**, 49 (1945).

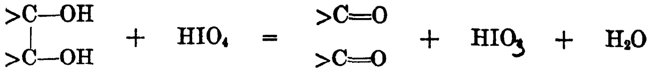
[103] Karrer and Mayer, *Helv. Chim. Acta*, **20**, 407 (1937).

[104] Malaprade, *Bull. soc. chim.*, **43**, 683 (1928).

[105] Fleury and Lange, *Compt. rend.*, **195**, 1395 (1932); *J. pharm. chim.*, **17**, 313 (1933).

[106] Fleury and Paris, *Compt. rend.* **196**, 1416 (1933); *J. pharm. chim.*, **18**, 570 (1933).

[107] Fleury and Fantome, *J. pharm. chim.*, **21**, 247 (1935).



$$\begin{array}{l}>C{-}OH\\ \quad|\\ >C{-}OH\end{array} + HIO_4 = \begin{array}{l}>C{=}O\\ \\ >C{=}O\end{array} + HIO_3 + H_2O$$

Substitutions, additions, and dehydrogenations (except for the easily accomplished dehydrogenation of hydroquinone) do not occur with periodic acid. Its reactions are also far more specific than those of lead tetraacetate. Again only the preparative applications of periodic acid shall be discussed, although important uses exist in the analytical domain.

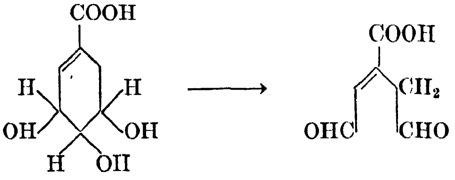
The free periodic acid obtained electrolytically,[108] or from silver periodate and chlorine,[109] can be used for oxidations. It is convenient to proceed from the easily prepared sodium or potassium salts, $Na_2H_3IO_6$ or KIO_4, from which periodic acid solution is prepared by adding the calculated amount of sulfuric acid. Water serves best as a solvent, but the organic component can be dissolved as well in methanol, dioxane, or glacial acetic acid. The speed of the oxidation depends greatly on the pH, proceeding more rapidly in the acid region.[110]

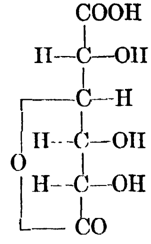
In principle one can carry out with periodic acid all the oxidative glycol fissions as with lead tetraacetate. Karrer[111] compared both oxidizing agents in two simple examples and found them equally suitable from a preparative standpoint. Nevertheless important differences exist in individual compounds and the account shall be limited to these.

The rates with which simple glycols are oxidized by these oxidizing agents are very different and stand in no simple relation to each other.[49] Periodic acid oxidizes ditertiary glycols very slowly, so that often, especially in the presence of aromatic substituents, no reaction at all is to be noticed. Besides, the danger of the pinacol rearrangement, because of the acid used must be reckoned with. The opposite is true of ethylene glycol and α derivatives of the glycerols; here periodic acid is markedly superior to lead tetraacetate.[112] If more than two hydroxyl groups stand in neighboring positions, as in free glycerol or in mannitol, cleavage occurs at all the C—C bonds. A middle —CHOH— group is oxidized by periodic acid to formic acid and by lead tetraacetate to CO_2. These facts must be considered in calculating the amount of oxidizing agent to be used. The free sugars behave toward the periodic acid as if they were aliphatic hydroxyaldehydes, that is, fission occurs between all the C atoms.[104,105] In contrast with the lead tetraacetate, on the other hand, the lactol ring is stable.[113] Glycosides

[108] Willard and Ralston, *Trans. Electrochem. Soc.*, **62**, 239 (1932).
[109] Malprade, *Bull. soc. chim.*, **39**, 330 (1926).
[110] Price and Kroll, *J. Am. Chem. Soc.*, **60**, 2726 (1938).
[111] Karrer and Hirohata, *Helv. Chim. Acta*, **16**, 959 (1933).
[112] Pyman and Stevenson, *J. Chem. Soc.*, **1934**, 448.
[113] Criegee, *Ann.*, **495**, 211 (1932).

act in both cases as ring compounds.[114] For the oxidation of acetone sugars lead tetraacetate is preferred, because periodic acid can split off the easily hydrolyzed acetone residue. The opposite is true in the oxidation of shikimic acid (LXI) to the dialdehyde (LXII).[115] Lead tetraacetate is useless in this case, because it would substitute the reaction product at the active methylene group.


(LXI) (LXII)


(LXIII)

A distinction worthy of notice applies to the α-hydroxy acids. These are not noticeably affected by periodic acid in the cold. As an example, lead tetraacetate splits tartaric acid between all four C atoms, while periodic acid produces glyoxylic acid[104] quite smoothly; the same applies to the gluconic and saccharic acids[105] as well as to their monolactones (LXIII), which, according to Schmidt and Gunther,[116] are attacked only in the 4,5 position by periodic acid even though the 1,2 position is a possible point of attack.

α-Hydroxyaldehydes and α-hydroxyketones are, in contrast to α-hydroxy acids, oxidized smoothly even in the cold by periodic acid, $R{-}COCHOH{-}R' \rightarrow R'COOH + R'{-}CHO$.[117,118] Since a carboxylic acid appears as a fission product, a difference between the action of lead tetraacetate and periodic acid upon polyhydroxy compounds emerges. Thus the oxidation of a sterol derivative with the side chain $>C(OH){-}CO{-}CH_2OH$ stops at the stage of the hydroxy acid $>C(OH){-}COOH$ with periodic acid, while with lead tetraacetate this oxidation produces the ketone, $>C{-}O$, without identifiable intermediate reaction products.[119] On the contrary, with the isomeric side chain $-CO{-}CH(OH){-}CH_2OH$, the course of the one-step reaction is identical with both oxidizing agents,[120] resulting in the acid R—COOH, because periodic acid is able to split the possible intermediate product R—CO—CHO, the same as it does any α-ketoaldehyde. α-Diketones are attacked only slowly to give, by the splitting of the C—C chain, 2 moles of monocarboxylic acid.[117] According to the work of Nicolet and Shinn[121] α-hydroxylamines are also oxidized like the glycols. Since the α-amino acids react at least a thousand times more slowly than the α-hydroxy acids, formaldehyde and glyoxylic acid originate, for example, from serine, $CH_2(OH)—CH(NH_2)—COOH$, by division between the α and β- —C— atoms. Diethanolamine, $CH_2(OH)—CH_2—NH—CH_2—CH_2OH$, decomposes in a fast reaction into 4 moles of formaldehyde and 1 mole of NH_3. At first the division probably proceeds in one place forming CH_2O and $CH_2{=}N—CH_2OH$; this decomposes under hydrolysis into a second mole of CH_2O and $H_2N—CH_2—CH_2OH$, which is oxidized by periodic acid to $HN{=}CH_2$ and CH_2O, whereupon the imine finally decomposes into NH_3 and CH_2O. If the nitrogen atom in an α-hydroxyamine is tertiary, there is no oxidation, $(C_2H_5)_2N—CH_2—CH_2OH$ being stable.

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[114] Jackson and Judson, *J. Am. Chem. Soc.*, **58**, 378 (1936); **59**, 994 (1937); **61**, 959 (1939). Maclay and Hudson, *ibid.*, **60**, 2059 (1938); **61**, 1660 (1939). Clenahan and Hocket, *ibid.*, **60**, 2061 (1938); **61**, 1667 (1939). Hocket and Maynard, *ibid.*, **61**, 2111 (1939).

[115] H. O. L. Fischer and Daugschat, *Helv. Chim. Acta*, **18**, 1204 (1935).

[116] Schmidt and Gunther, *Ber.*, **71**, 493 (1938).

[117] Clutterbuck and Reuter, *J. Chem. Soc.*, **1935**, 1467.

[118] King, *J. Chem. Soc.*, **1936**, 1788.

[119] Reichstein, *Helv. Chim. Acta*, **20**, 978 (1937). Reichstein, Meystre, and Euw, *ibid.*, **22**, 1107 (1939).

In closing, periodic acid possesses a plain superiority for the oxidation of compounds which are soluble only in water and which are oxidized with difficulty. In these cases the earlier mentioned oxidation with lead tetraacetate in aqueous medium cannot be used. Thus the oxidative degradation of the starches, investigated by Jackson and Hudson[122] and others,[123] is possible only with periodic acid.

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[120] Raistrick and Smith, *Biochem. J.*, **29**, 606 (1935).

[121] Nicolet and Shinn, *J. Am. Chem. Soc.*, **61**, 1615 (1939).

[122] Jackson and Hudson, *J. Am. Chem. Soc.*, **59**, 2049 (1937).

[123] Caldwell and Hixon, *J. Biol. Chem.*, **123**, 595 (1933). Grangard, Michell, and Purves, *J. Am. Chem. Soc.*, **61**, 1290 (1939).

Dehydrogenation with Sulfur, Selenium, and Platinum Metals

By P. A. PLATTNER

Translated and revised by E. C. ARMSTRONG

During the past twenty-five years, dehydrogenation has been established as a most useful aid in studying the constitution of organic natural products. The method achieved its first great success in polyterpene research, and since 1921 has been systematically used and developed in this field by Ruzicka.[1] It was well known at that time that the naphthalene hydrocarbons cadalene[2,3] and eudalene[3] could be obtained from some sesquiterpenes by dehydrogenation with sulfur. The same procedure applied to simple terpenes, such as limonene and terpinene, resulted in the formation of *p*-cymene,[3] which had long been recognized as the parent aromatic hydrocarbon of these terpenes.

It had previously been proposed, first by Wallach[4] and later by Semmler,[5] that certain sesquiterpenes might be hydrogenated naphthalene derivatives. The dehydrogenation results obtained by Ruzicka confirmed this hypothesis in a manner surprisingly straightforward from the experimental standpoint. Further insight into the structure of the carbon residues of the sesquiterpenes in question was soon provided by the identification of cadalene, both by analysis and by synthesis, as 1,6-dimethyl-4-isopropylnaphthalene,[6] and eudalene as 1-methyl-7-isopropylnaphthalene.[7]

The results obtained in the sesquiterpene series furnished the basis for further applications of dehydrogenation methods. The conversion of diterpenes, such as abietic acid, *d*-pimaric acid, and agathenedicarboxylic acid, into phenanthrene derivatives has helped to establish the constitution of these compounds. The same holds true for the chemistry of the triterpenes, some of which can be classified as hydrogenated picene derivatives, on the basis of dehydrogenation results.[8]

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[1] L. Ruzicka, *Fortschr. Chem., Physik physik. Chem.*, **19A**, No. 5 (1928), 57 pp. (*Constitution and Relationships in the Sesquiterpene Series*).

[2] L. Ruzicka and J. Meyer, *Helv. Chim. Acta*, **4**, 505 (1921).

[3] L. Ruzicka, J. Meyer, and Mingazzini, *Helv. Chim. Acta*, **5**, 345 (1922).

[4] Wallach, *Ann.*, **239**, 49 (1887).

[5] Semmler and Becker, *Ber.*, **46B**, 1817 (1913). Semmler and Stenzel, *ibid.*, **47B**, 2557 (1914).

[6] L. Ruzicka and Seidel, *Helv. Chim. Acta*, **5**, 369 (1922).

[7] L. Ruzicka and Stoll, *Helv. Chim. Acta*, **5**, 923 (1922).

Successful applications of these methods have not, however, been confined solely to polyterpene chemistry. For example, the dehydrogenation of cholesterol and cholic acid has played an important part in determining the structure of the sterols. In 1932, the results of such experiments led Rosenheim and King,[9] and Wieland and Dane[10] to a new and now generally accepted formulation of the entire sterol chemistry. Dehydrogenation is largely responsible for the advances made during the last few years in the fields of the sterols and bile acids, the sex hormones, the D vitamins, the cardiac aglucons, and the carcinogenic hydrocarbons. The method has also been applied successfully to the investigation of other natural products such as alkaloids, and its field of usefulness is likely to be expanded still further in the future. Depending on the desired goal, emphasis may be placed on either the synthetic or the analytic aspect of these investigations. Although dehydrogenation reactions have been used to an increasing extent, during the last few years, in the synthesis of polycyclic aromatic compounds, their principal value is still in determining the constitution of organic natural products. This application will therefore be considered first.

The fundamentals of this work can be outlined as follows.[1] It is extremely difficult and time-consuming to establish the structure of the high molecular weight alicyclic compounds by the ordinary systematic methods of analysis. If these substances can be converted, in an unequivocal manner, into the parent aromatic compounds, then such questions as the relative positions of the rings and of the substituents can be answered comparatively easily, and a large number of possible isomers can be eliminated from consideration. Furthermore, the parent aromatic compounds exhibit typical properties, absorption spectra for example, and also are much more readily identified by synthesis than are the hydrogenated derivatives. In a familiar ring system it is much easier to determine the positions of the carbon-to-carbon double bonds and of the substituents, and to establish the stereochemical relationships.

I. SCOPE OF DEHYDROGENATION METHODS

Inasmuch as we are considering dehydrogenation essentially as an aid in determining the constitution of organic compounds, we can omit an exhaustive discussion of the theoretical basis for the formation of unsaturated and aromatic systems from more completely hydrogenated compounds. It also seems sufficient to confine the discussion of the products of dehydrogenation reactions almost exclusively to aromatic compounds, that is, derivatives of benzene and condensed benzene ring systems, and the completely dehydrogenated, so called aromatic, heterocyclic compounds with five- and six-membered rings, such as thiophene and pyridine.[11] The azulenes,[12] of which the nucleus is the *naphthalene type* combination of a five- and a seven-membered ring, form a supplement to these well known aromatic systems which is extremely interesting from the theoretical standpoint. In contrast to the azulene structure, isolated five- and seven-membered rings generally are not dehydrogenated even when, as in indane for example, they are combined with a benzene ring. Likewise, double bonds cannot be introduced into the longer aliphatic chains by the usual dehydrogenation methods, except in a few special cases. The behavior toward dehydrogenation reagents of these compounds which cannot be dehydrogenated will be briefly discussed for the individual case.

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[8] L. Ruzicka, *Angew. Chem.*, 51, 5–11 (1938).

[9] Rosenheim and King, *Chemistry and Industry*, 51, 464–466, 954–956 (1932).

[10] Wieland and Dane, *Z. physiol. Chem.*, 210, 268–281 (1932). Wieland, Dane, and Martius, *ibid.*, 215, 15–24 (1933).

Oxidation processes, which on the basis of their probable reaction mechanisms were formerly classed as dehydrogenations, will not be discussed.

II. VARIOUS DEHYDROGENATION METHODS AND REAGENTS

Dehydrogenation reactions have been used intermittently for a long time. The exhaustive bromination method of von Baeyer and Villiger,[13] which was used successfully in investigating the terpene series, and the dehydrogenative decomposition with manganese dioxide and sulfuric acid[14,15] are two early methods which have practically no application at the present time.

Catalytic dehydrogenation in the vapor phase, especially with nickel catalysts, was introduced as a general method by Sabatier and Senderens[16] at the beginning of this century. It was improved and systematically investigated by Zelinsky[17] through the use of platinum metal catalysts. Since nickel requires very high reaction temperatures and therefore readily causes splitting out of carbon atoms and other side reactions, palladium and platinum catalysts are generally much better. There seems to be no fundamental difference between the action of palladium and that of platinum.

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[11] Hückel, *Theoretische Grundlagen der organischen Chemie*, Akadem. Verlagsgesellschaft, Leipzig, 1931, Vol. I, 365 ff.

[12] Plattner and Pfau, *Helv. Chim. Acta*, **20**, 224–232 (1937).

[13] von Baeyer and Villiger, *Ber.*, **32 B**, 2429–2447 (1899).

[14] See also L. Ruzicka, Schinz, and J. Meyer, *Helv. Chim. Acta*, **6**, 1077 (1923).

[15] L. Ruzicka and Rudolph, *Helv. Chim. Acta*, **10**, 915–920 (1927).

[16] Sabatier, *Catalytic Hydrogenation* (German), Akadem. Verlagsgesellschaft, Leipzig, 1914.

[17] Zelinsky, *Ber.*, **44 B**, 3121–3125 (1911).

Other platinum metals, such as ruthenium, rhodium, iridium, and osmium, have been tried by Zelinsky and Turova-Pollak.[18,19]

The systematic use of sulfur as a dehydrogenation reagent dates back, as previously mentioned, to Ruzicka.[1-3] Even before that, Curie,[20] Kelbe,[21] and Vesterberg[22] had used sulfur in the dehydrogenation of rosin and the abietic acids derived from it, and had thereby obtained retene, but the general importance of this method was not realized at that time.[1]

The use of selenium for dehydrogenation was introduced by Diels[23] and was quickly adopted, since selenium has a number of advantages over sulfur. On the other hand, the relatively high dehydrogenation temperatures necessitated by the use of selenium also involve various disadvantages.

In addition to these common reagents, various others have occasionally been used.[24] It is interesting to note that activated charcoal, which is often used as a carrier for the platinum metal catalysts, can cause dehydrogenation by itself.[25-27] Under favorable conditions, even atmospheric oxygen,[28] selenium dioxide,[29] concentrated sulfuric acid,[30] etc., can effect dehydrogenation. The use of dialkyl sulfides instead of sulfur for dehydrogenation was proposed by Ritter and Sharpe.[31] Chloranil was introduced as a mild dehydrogenation agent by Arnold and Collins,[32] and has since been used by Barclay and Campbell[33] for the dehydrogenation of carbazole and its derivatives, and by Crawford and Nelson[34] for the preparation of 2,3-diphenylnaphthalene from the 3,4-dihydro compound. Other experiments with these reagents have not been successful, however; so their use in the degradation of natural products is open to question.

III. REACTION MECHANISMS

Little is actually known about the reaction mechanism of dehydrogenation. The problem is complicated by the fact that entirely normal dehy-

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[18] Zelinsky and Turova-Pollak, *Ber.*, **58 B**, 1298 (1925).
[19] *Ber.*, **62 B**, 2865 (1929).
[20] P. Curie, *Chem. News*, **30**, 189 (1874).
[21] Kelbe, *Ber.*, **11**, 2174 (1878).
[22] Vesterberg, *Ber.*, **36 B**, 4200 (1903).
[23] See the summarized lecture, *Ber.*, **69 A**, 195 (1936).
[24] See, for example, H. Meyer, *Analyse und Konstitutionsermittlung organischer Chemie*, 6th ed., Springer, Berlin, 1938.
[25] Bahr, *Ber.*, **64 B**, 2258 (1931).
[26] Asahina and Nakanishi, *J. Pharm. Soc. Japan*, **48**, 1–20 (1928).
[27] Heisel and Dewein, German Patent, 701,514; *cf. Chem. Abstracts*, **35**, 8310 (1941).
[28] *E.g.*, Lewis, Ramadge, and R. Robinson, *J. Chem. Soc.*, **1935**, 1412–1414.
[29] Borgwardt and Schwenk, *J. Am. Chem. Soc.*, **56**, 1185–1187 (1934). See also Stein, *Angew. Chem.*, **54**, 146 (1941).
[30] *E.g.*, J. W. Cook and Hewett, *J. Chem. Soc.*, **1933**, 1098–1111.
[31] Ritter and Sharpe, *J. Am. Chem. Soc.*, **59**, 2351–2352 (1937).
[32] Arnold and Collins, *J. Am. Chem. Soc.*, **61**, 1407–1408 (1939).
[33] Barclay and Campbell, *J. Chem. Soc.*, **1945**, 530–533.
[34] Crawford and Nelson, *J. Am. Chem. Soc.*, **68**, 134–135 (1946).

drogenations, those in which no cleavage, formation, or rearrangement of carbon-to-carbon bonds occurs, are relatively rare. In most cases, indeed, the real dehydrogenation reaction is accompanied by partial thermal effects, such as cleavage of quaternary methyl groups. Attempts have been made to investigate the thermal decomposition and the dehydrogenation separately,[35,36] but such a procedure, probably justly, has found no general application in the actual determination of constitution.

Catalytic dehydrogenations are probably based on fundamentally different reactions than are the dehydrogenations with sulfur and selenium. In the final effect, however, the dissimilarities in these three most common methods are not very important and seem to be due for the most part to the different reaction temperatures. Separate treatment of the three methods can therefore logically be omitted. However, the peculiarities of the individual reagents will be noted, where necessary, in the course of the detailed discussion.

Originally, dehydrogenation reactions were confined almost exclusively to hydrocarbons, but recently compounds containing functional groups, such as hydroxyl, have found increasing use as starting materials. In many cases the reaction products formed from these compounds are different from those obtained from the parent hydrocarbons; so much broader conclusions may be drawn from the dehydrogenation results. Also, it is often possible to preserve the functional groups during dehydrogenation, or at least to detect them in recognizable form in the final products. Keto groups, for example, can be converted into phenolic hydroxyl groups. Since the course of the dehydrogenation is often considerably influenced by the functional groups present, their behavior in dehydrogenation reactions will be dealt with first.

IV. BEHAVIOR OF FUNCTIONAL GROUPS

As might be expected, *tertiary hydroxyl groups* are readily split off during dehydrogenation. In general, the products are identical with those obtained from the hydrocarbon, as is shown by the formation of eudalene from eudesmol by direct dehydrogenation with sulfur,[3] and from 2-(hydroxyisopropyl)-8-methyl-1,2,3,4-tetrahydronaphthalene by dehydrogenation with selenium.[37] Catalytic dehydrogenation with palladium-charcoal readily removes tertiary hydroxyl groups attached directly to a saturated ring system.[38,39]

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[35] L. Ruzicka, Huyser, Pfeiffer, and Seidel, *Ann.*, **471**, 21 (1929).

[36] L. Ruzicka and van Veen, *Rec. trav. chim.*, **48**, 1018–1024 (1929).

[37] Chakravarti, *J. Indian Chem. Soc.*, **20**, 393–398 (1943).

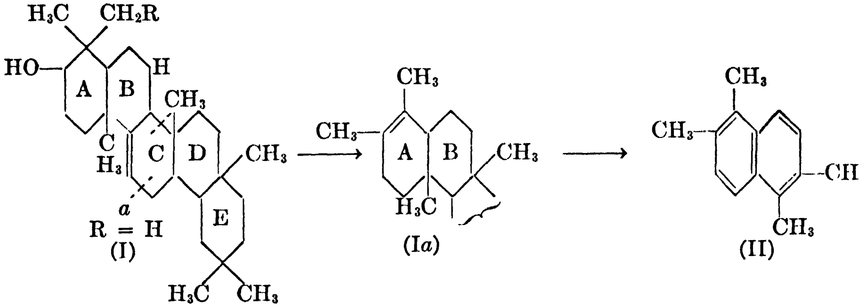
[38] Bachmann and Wilds, *J. Am. Chem. Soc.*, **60**, 624–627 (1938).

[39] W. S. Johnson, Goldman, and Schneider, *J. Am. Chem. Soc.*, **67**, 1357–1360 (1945).

Secondary hydroxyl groups are often split off in the form of water before the real dehydrogenation begins. To avoid the frothing which accompanies it, the removal of the water is best carried out carefully in the reaction vessel prior to the true dehydrogenation, as recommended by Ruzicka and co-workers in the selenium dehydrogenation of cholic acid. The composition of the products is not altered by this procedure.[40] At the relatively high temperatures of selenium dehydrogenations, secondary hydroxyl groups are usually eliminated, and the products are almost exclusively hydrocarbons. For example, cyclopentenophenanthrene derivatives are obtained by the selenium dehydrogenation of androstenediols.[41] In the triterpene series such dehydrogenation products as 1,2,5,6-tetramethylnaphthalene (II) appear, the formation of which must be explained by retropinacoline rearrangement according to Formulas I, I*a*, and II.[42,43]

Surprisingly, the acetates of triterpene alcohols appear to behave differently, since in their dehydrogenation the retropinacoline rearrangement is strongly repressed.[44,45]

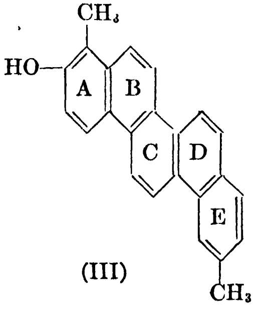
Although in general hydrocarbons are the chief products of dehydro-



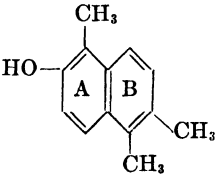
(I)

(I*a*)

(II)



(III)



(IV)

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[40] L. Ruzicka, Goldberg, and Thomann, *Helv. Chim. Acta*, **16**, 813 (1933).

[41] Butenandt and Surány, *Ber.*, **75 B**, 597–606 (1942).

[42] L. Ruzicka, Goldberg, and K. Hofmann, *Helv. Chim. Acta*, **20**, 325–328 (1937).

[43] L. Ruzicka, Schellenberg, and Goldberg, *Helv. Chim. Acta*, **20**, 791–804 (1937).

[44] L. Ruzicka and Lamberton, *Helv. Chim. Acta*, **23**, 1338–1345 (1940).

[45] L. Ruzicka and Rosenkranz, *Helv. Chim. Acta*, **23**, 1311–1324 (1940).

genations carried out under such relatively vigorous conditions, it is also usually possible to detect certain amounts of oxygen-containing compounds, such as phenols. One of the most notable examples of this was the isolation of 1,8-dimethyl-2-hydroxypicene (III)[42,43] from the dehydrogenation of amyrenes. The constitution of this product was established by the synthesis of the methyl ether.[46] By this reaction the relative positions of the 24 carbon atoms and the characteristic hydroxyl groups of the corresponding triterpenes were conclusively established. A trimethylnaphthol,[47,48] which was later identified as hydroxyagathalene (IV) (1,2,5-trimethyl-6-hydroxynaphthalene),[49,50] and which is formed from the Rings A and B (Formula I) of the triterpene, was obtained as an additional phenolic dehydrogenation product from most of the triterpenes. Mention should also be made of the formation of 7-hydroxy-1-methylphenanthrene from the diterpene alcohol totarol,[51] and of 9-phenanthrol from 9-hydroxyoctahydrophenanthrene.[52] An example of a similar dehydrogenation carried out under very mild conditions is the conversion of neoergosterol (VI) into a naphthol derivative (VII).[53] Secondary hydroxyl groups protected by methylation may be unaffected even by selenium dehydrogenation.[54]

Cyclic ketones are very readily converted to phenols by dehydrogenation. This reaction was thoroughly studied by Darzens and Lévy,[55] who obtained phenol from cyclohexanone, and α-naphthol from α-tetralone, by dehydrogenation with sulfur or selenium. Ruzicka[56] has investigated the dehydrogenation of *trans*-β-decalone and 3-methylcyclohexanone. Horning[57] obtained the corresponding phenols from some alkylcyclohexanones by refluxing with sulfur for 1 hour; the yields were 26 to 29%. According to Fieser, Hershberg, and Newman,[58] the corresponding hydroxybenzopyrene is obtained from the ketone (V) in about 20% yield by a short dehydrogenation with sulfur at low temperatures (220° to 230° C.); with selenium at 310° to 320°C., however, 1,2-benzopyrene is the main product, only traces of the hydroxyl derivatives being isolated.

A number of examples are known of the formation of phenols by the

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[46] L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **20**, 1155–1164 (1937).

[47] L. Ruzicka, Brüngger, Egli, Ehmann, Furter, and Hösli, *Helv. Chim. Acta*, **15**, 431–457 (1932).

[48] L. Ruzicka, Hösli, and K. Hofmann, *Helv. Chim. Acta*, **19**, 370–377 (1936).

[49] L. Ruzicka, K. Hofmann, and Frei, *Helv. Chim. Acta*, **19**, 386–392 (1936).

[50] L. Ruzicka, K. Hofmann, and Schellenberg, *Helv. Chim. Acta*, **19**, 1391–1402 (1936).

[51] Short and Stromberg, *J. Chem. Soc.*, **1937**, 516–520.

[52] J. W. Cook, Hewett, and Lawrence, *J. Chem. Soc.*, **1936**, 71–80.

[53] Honigmann, *Ann.*, **511**, 292–301 (1934).

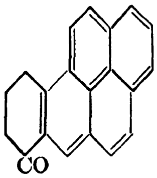
[54] L. Ruzicka, Rey, and Smith, *Helv. Chim. Acta*, **26**, 2057–2063 (1943).

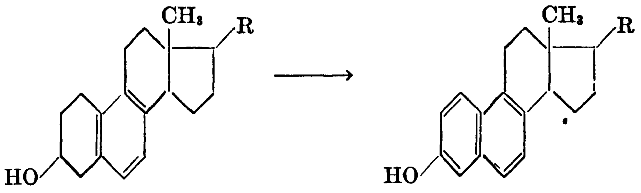
[55] Darzens and Lévy, *Compt. rend.*, **194**, 181–183 (1932) and later articles.

[56] L. Ruzicka, *Helv. Chim. Acta*, **19**, 419–423 (1936).

[57] Horning, *J. Am. Chem. Soc.*, **67**, 1421–1422 (1945).

[58] L. F. Fieser, Hershberg, and Newman, *J. Am. Chem. Soc.*, **57**, 1509–1510 (1935).


(V)



(VI) (VII)

catalytic dehydrogenation of cyclic ketones. 7-Methyl-1-naphthol is obtained from 7-methyl-1-tetralone with palladium,[59] thymol from piperitone with nickel[60] or palladium,[61] and chrysenols from ketohexahydrochrysenes also by the use of palladium.[62,63]

Some dehydrogenations of this type have been investigated in detail by Linstead and Michaelis.[64] *α*-Tetralone, *ar*- and *ac*-*β*-tetralol, *trans*-*α*-decalone, *cis*- and *trans*-*β*-decalone, *cis*- and *trans*-*β*-decalol all give the corresponding naphthol in yields of 12 to 60%, along with varying amounts of naphthalene. The compounds which are already most nearly in the aromatic state can be dehydrogenated under milder conditions and give correspondingly more naphthol and less naphthalene. The investigation has also been extended to terpene ketones,[65] which can be converted to thymol and carvacrol in very good yields.

Extracyclic keto groups, on the other hand, are often unaffected by dehydrogenation under relatively mild conditions. According to Barbot,[66] for example, *β*-acetyltetralin can be converted by sulfur into methyl naphthyl ketone in 70% yield. It is interesting to note that anthraquinones are readily obtained by the dehydrogenation of hydrogenated anthraquinones especially with sulfur.[67] Johnson and co-workers[68] converted 3′-keto-3,4-dihydro-1,2-cyclopentenonaphthalene to 4,5-benzhydrindone-1 by dehydrogenation with sulfur for 1 hour at 220°C.

The catalytic dehydrogenation of some ketones derived from tetrahydronaphthalene has been investigated by Newman and co-workers,[69,70] who dehydrogenated the following compounds with palladium-charcoal under fairly vigorous conditions: methyl 2-(5,6,7,8-tetrahydronaphthyl) ketone; methyl β-(5,6,7,8-tetrahydro-2-naphthoyl)propionate; methyl 1-(1,2,3,4-tetrahydronaphthyl) ketone; 1-(1,2,3,4-tetrahydro)naphthyl-2-propanone; and 1-(1,2,3,4-tetrahydro-1-naphthyl)-3-butanone. The results indicate that the course of the reaction is greatly influenced by the position of the carbonyl group in the side chain and in relation to the hydrogenated structure. The carbonyl groups in the first two of the above compounds were reduced to methylene groups; the last three compounds exhibited no reduction of the carbonyl groups. Methyl 1-(1,2,3,4-tetrahydronaphthyl)ketone and 1-(1,2,3,4-tetrahydro-1-naphthyl)-3-butanone resisted dehydrogenation, most of the starting material being recovered unchanged. 1-(1,2,3,4-Tetrahydro)naphthyl-2-propanone was smoothly dehydrogenated to the naphthyl ketone in a yield of 84%.

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[59] L. Ruzicka and Mörgeli, *Helv. Chim. Acta*, 19, 377–386 (1936).

[60] Treibs and Schmidt, *Ber.*, 60 B, 2335–2341 (1927).

[61] Read, Watters, Robertson, and Hughesdon, *J. Chem. Soc.*, 1929, 2068.

[62] Wilds and Shunk, *J. Am. Chem. Soc.*, 65, 469–475 (1943).

[63] Cook and Schoental, *J. Chem. Soc.*, 1945, 288–293.

[64] Linstead and Michaelis, *J. Chem. Soc.*, 1940, 1134–1139.

[65] Linstead, Michaelis, and Thomas, *J. Chem. Soc.*, 1940, 1139–1147.

[66] Barbot, *Bull. soc. chim.*, 47, 1314–1323 (1930).

[67] L. F. Fieser and Seligman, *J. Am. Chem. Soc.*, 56, 2690–2696 (1934).

[68] W. S. Johnson, H. C. E. Johnson, and Petersen, *J. Am. Chem. Soc.*, 67, 1360–1366 (1945).

[69] Newman and Zahm, *J. Am. Chem. Soc.*, 65, 1097–1101 (1943).

[70] Newman and O'Leary, *J. Am. Chem. Soc.*, 68, 258–261 (1946).

From the fact that phenols are often obtained as products of the dehydrogenation of cyclic ketones, it is understandable that free and especially methylated *phenolic hydroxyl groups* are often unaffected by dehydrogenation. This is especially true of dehydrogenations with sulfur.[71–74] With selenium, the elimination of hydroxyl and methoxyl groups has been reported,[72,75] as well as instances in which these groups were retained,[76–80] which indicated that dehydrogenation temperatures above 300°C. promote the elimination. The examples given by Kon and Ruzicka,[81] especially, confirm this.

In general, phenolic oxygen atoms are more likely to be eliminated during dehydrogenation at the higher reaction temperatures. At the present time there is no definite information about the effect of the position of the oxygen atoms on the ease of elimination.

Examples of dehydrogenations of compounds containing *primary hydroxyl groups* are not very numerous. By the dehydrogenation of abietinol (VIII),[82] Ruzicka and Meyer[83] obtained retene (IX), which is also formed from abietic acid itself[83] and from methylabietene (X).[84] On the

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[71] L. F. Fieser and Holmes, *J. Am. Chem. Soc.*, **58**, 2319–2322 (1936).

[72] Haberland, *Ber.*, **69 B**, 1380–1386 (1936).

[73] Darzens and G. Lévy, *Compt. rend.*, **200**, 469–471 (1935).

[74] C. K. Chuang, Y.-L. Tien, and Y.-T. Huang, *Ber.*, **70 B**, 858–863 (1937). Hill, Short, and Stromberg, *J. Chem. Soc.*, **1937**, 1619–1622.

[75] Chatterjee, *J. Indian Chem. Soc.*, **13**, 659 (1936).

[76] Short, Stromberg, and Wiles, *J. Chem. Soc.*, **1936**, 319–322.

[77] Hill, Short, and Higginbottom, *J. Chem. Soc.*, **1936**, 317–319.

[78] Haworth and Sheldrick, *J. Chem. Soc.*, **1934**, 864–867.

[79] L. Ruzicka and H. Waldmann, *Helv. Chim. Acta*, **15**, 907–914 (1932).

[80] Butenandt, Weidlich, and Thompson, *Ber.*, **66 B**, 601 (1933).

[81] Kon and F. C. J. Ruzicka, *J. Chem. Soc.*, **1936**, 187–192.

[82] Formula of abietic acid according to L. Ruzicka and Sternbach, *Helv. Chim. Acta*, **21**, 565–583 (1938).

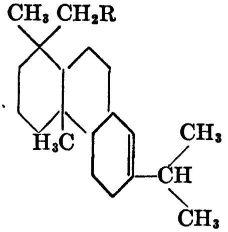
[83] L. Ruzicka and J. Meyer, *Helv. Chim. Acta*, **5**, 581 (1922).

[84] L. Ruzicka, Waldmann, P. J. Meyer, and Hösli, *Helv. Chim. Acta*, **16**, 169–181 (1933). The methylabietene (X) was obtained from abietinol through the corresponding aldehyde and reduction of the semicarbazone by the Wolff-Kishner method.

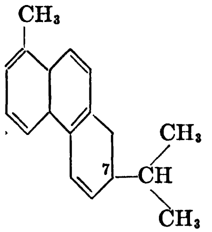
other hand, if water is first split out of abietinol, the main product is a homoretene,[83] which has been identified as 1-ethyl-7-isopropylphenanthrene.[85,86] Similar relationships have also been observed in the dehydrogenation of *d*-pimaric acid.[85–87] Therefore, during the elimination of water from abietinol (VIII), a retropinacoline rearrangement takes place, which results in the formation of XI; this rearrangement does not occur during the direct dehydrogenation. Also, retropinacoline rearrangement to an ethyl derivative does not seem to result from the dehydrogenation of hederagenin (I, R = OH).[88] Derivatives which would correspond to homoretene and to homopimanthrene (1-ethyl-7-methylphenanthrene) cannot be isolated for this reason.[89]

In connection with the dehydrogenation of hederagenin, it is interesting to note that there seems to be no migration of one of the geminal methyl groups, which in other cases results in the formation of 1,2,5,6-tetramethylnaphthalene, [42,43] indicating that this product is not formed when one of the geminal methyl groups carries an oxygen atom. This is true of the dehydrogenation of the corresponding aldehyde, gypsogenin,[88,90] as well as of hederagenin itself.

Newman and co-workers[69,70] investigated the behavior of some primary alcohols in connection with their study of the catalytic dehydrogenation of substituted tetrahydronaphthalenes. As in the case of the ketones, the reaction of the primary hydroxyl group appears to depend on its position relative to the hydrogenated structure.



(VIII) R = OH
(X) R = H



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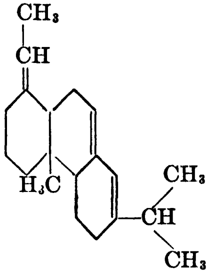

(XI)

A great many compounds containing free and also esterified *carboxyl groups* have been dehydrogenated. The formation of retene from abietic

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[85] L. Ruzicka, de Graaff, and Müller, *Helv. Chim. Acta*, **15**, 1300–1303 (1932).

[86] Haworth, *J. Chem. Soc.*, 1932, 2717–2720.

[87] L. Ruzicka and Balas, *Helv. Chim. Acta*, **7**, 875 (1924).

[88] For the constitution of hederagenin and gypsogenin, see L. Ruzicka and Giacomello, *Helv. Chim. Acta*, **20**, 299–309 (1937).

[89] L. Ruzicka, Hösli, and Ehmann, *Helv. Chim. Acta*, **17**, 442–455 (1934).

[90] L. Ruzicka, Brüngger, Egli, Ehmann, and Goldberg, *Helv. Chim. Acta*, **15**, 1496–1506 (1932)

acid by dehydrogenation with sulfur, which was one of the first dehydrogenation reactions to be thoroughly investigated, shows that decarboxylation can readily occur under these conditions. Experience in a number of analogous cases indicates that a carboxyl group on a quaternary carbon atom is readily split off, even when it is esterified.[75,87] This is confirmed not only by the behavior of natural products but also by the results of synthetic work.[91,92]

Secondary and primary carboxyl groups, on the other hand, are very likely to be retained during dehydrogenation. Probably the first application of this tendency was made by Darzens and Lévy[93] in the preparation of 1-methyl-7-isopropyl-3-naphthoic acid from the corresponding 1,2,3,4-tetrahydro compound by dehydrogenation with sulfur at 230° to 240°C. 4-Methyl-α-naphthoic acid, however, could not be prepared in this way, since carbon dioxide was always split out during dehydrogenation.[94] The procedure was later extended to phenanthrenecarboxylic acids[95] and in recent years has frequently been applied to preparative work. Examples of its application are found in the work of Darzens and Lévy,[96–98] of Fieser and Hershberg,[71,99,100] of Cohen and co-workers,[101–103] and of Newman.[104] The dehydrogenation with palladium-charcoal of esters of some tetrahydronaphthylcarboxylic acids was studied by Newman and co-workers.[69,70] Even under the fairly vigorous conditions employed, smooth conversion to the corresponding naphthyl derivative resulted. The same procedure was applied by Johnson and co-workers[68] in the preparation of β-1-naphthylpropionic acid and 1-naphthylsuccinic acid from the 3,4-dihydro compounds. In general, sulfur, palladium, and platinum are better than selenium for such dehydrogenations, since selenium readily causes decarboxylation, probably because of the higher dehydrogenation temperatures.

It is not surprising that side reactions often accompany the dehydrogenation of carboxylic acids and their functional derivatives. Thus it has been observed that free carboxylic acids are formed from esters, and anhydrides from dicarboxylic acids.[56,105]

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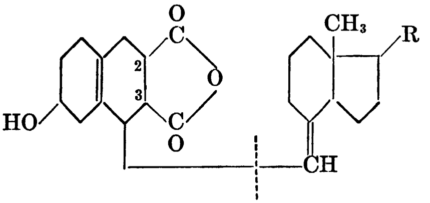
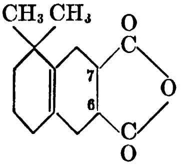
[91] Bardhan and Sen-Gupta, *J. Chem. Soc.*, **1932,** 2520.
[92] J. W. Cook, Haslewood, and A. M. Robinson, *J. Chem. Soc.*, **1935,** 667–671.
[93] Darzens and A. Lévy, *Compt. rend.*, **194,** 2056 (1932).
[94] Darzens and A. Lévy, *Compt. rend.*, **199,** 1131–1133 (1934).
[95] Darzens and A. Lévy, *Compt. rend.*, **200,** 2187–2189 (1935).
[96] Darzens and A. Lévy, *Compt. rend.*, **201,** 902–904 (1935).
[97] Darzens and A. Lévy, *Compt. rend.*, **202,** 427–428 (1936).
[98] Darzens and A. Lévy, *Compt. rend.*, **203,** 669–671 (1936).
[99] L. F. Fieser and Hershberg, *J. Am. Chem. Soc.*, **57,** 1508–1509 (1935).
[100] L. F. Fieser and Hershberg, *J. Am. Chem. Soc.*, **57,** 1851–1854 (1935).
[101] Cohen, *Nature*, **136,** 869–870 (1935).
[102] Cohen, Cook, and Hewett, *J. Chem. Soc.*, **1936,** 52–53.
[103] Cohen and Warren, *J. Chem. Soc.*, **1937,** 1315–1320.
[104] Newman, *J. Org. Chem.*, **9,** 518–528 (1944).
[105] Cartwright and Haworth, *J. Chem. Soc.*, **1944,** 535–537.

An interesting discovery is that carboxyl groups can be reduced to methyl groups in the course of their dehydrogenation, though this type of reaction seems so far to have been observed only in dehydrogenations with selenium. For example, Windaus and Thiele[106] obtained 2,3-dimethylnaphthalene from dihydro-vitamin D_2-maleic anhydride (XII).

According to Thiele and Trautmann,[107] 2,3-dimethylnaphthalene is also obtained from 2,3-naphthalic anhydride by treatment with selenium in the presence of *p*-cyclohexylphenol as a hydrogen donor. A somewhat similar reaction occurred with 1,8-naphthalic anhydride; one of the carboxyl groups was converted into a methyl group, while the other was eliminated, α-methylnaphthalene being formed. Ruzicka[56] has also reported a case of the same kind in which 1,6,7-trimethylnaphthalene was formed from the anhydride XIII with selenium at 350°C.



(XII)



(XIII)

In connection with these discussions on functional groups, the influence of ***double bonds*** already present in the molecule upon the result of the dehydrogenation must still be considered. As a rule, dehydrogenation goes more readily and in better yield, the more nearly the starting material is to being in the aromatic condition; that is, the more double bonds it already contains. In this respect the position of the double bonds can play an important part. For example, terpinene is converted to cymene in about 50% yield by dehydrogenation with sulfur, while the isomeric limonene gives a yield of only 15% under the same conditions.[3]

Not only do the position and number of the double bonds in the starting material generally have considerable influence on the yield of dehydrogenation products, but in some cases they can even determine the constitution of the products. It is known, for example, that the isomeric monocyclic sesquiterpenes bisabolene (XIV) and zingiberene (XV) behave differently on dehydrogenation in that the bicyclic compound, cadalene, results from zingiberene with sulfur,[3,108] while bisabolene, both with sulfur and with selenium, gives only benzenoid hydrocarbons (probably methylisooctylbenzene).[109]

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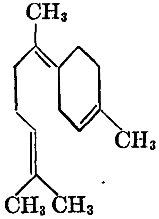
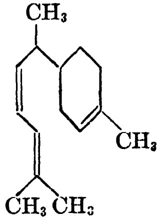
[106] Windaus and Thiele, *Ann.*, **521**, 160–175 (1936).
[107] Thiele and Trautmann, *Ber.*, **68 B**, 2245–2247 (1935).
[108] L. Ruzicka and van Veen, *Ann.*, **468**, 143–162 (1929).



(XIV)



(XV)

This is explainable by the different cyclization tendencies of these isomeric sesquiterpenes, and it may be assumed that in the case of zingiberene the cyclization precedes the dehydrogenation. In similar fashion it is also possible to explain the behavior of (bicyclic) agathenedicarboxylic acid (XXVIII),[110,111] which on dehydrogenation gives phenanthrene derivatives in addition to naphthalene derivatives.

Since, other things being equal, the ease of dehydrogenation is dependent on the number of double bonds already present in the molecule, perhydro compounds can be expected to dehydrogenate only with extreme difficulty. With the more volatile of these compounds, the boiling temperature under atmospheric pressure is not sufficient to effect dehydrogenation, and reaction in the vapor phase over a catalyst or in a sealed tube must be resorted to. These facts probably account for many of the contradictory statements found in the literature about the ease of dehydrogenation of such compounds.

V. HYDROGENATION EFFECTS

It is often impossible to determine whether the disappearance of the extracyclic double bond in such dehydrogenations as that of limonene to cymene is due to migration in the nucleus or to hydrogenation. The latter hypothesis is supported by the fact that similar hydrogenations have been proved in other cases. For example, indenes are converted to the corresponding indanes in the presence of selenium in a sealed tube at 350°C.[112] The hydrogenation of double bonds has been observed in the triterpene series,[89] contrary to normal hydrogenation procedure; the saturated hydrocarbon $C_{29}H_{50}$ was obtained from oleanoleic acid, and β-amyrene was partly converted into amyrane.[43] In a similar manner, Dorée and Petrov obtained cholestane from cholesterilene,[113] and cholestanone from cholesterol in 30 to 40% yields,[114] by heating with selenium at 250°C. In general, therefore, it can be expected that side chains and similar parts of molecules, such as attached five-membered rings, will be obtained in completely saturated form in the products of dehydrogenation. Aromatic compounds with unsaturated side chains or with attached, unsaturated five-membered rings, such as indene or acenaphthalene type combinations, cannot be expected as dehydrogenation products and have not, so far as is known, been detected with any certainty up to the present. This assumption is confirmed by the dehydrogenation of hexahydroindane to indane,[115] the isolation of γ-methylcyclopentenophenanthrene and methylcholanthrene, and also a number of experiments on compounds containing allyl side chains[116–119] and on a series of unsaturated fatty acids.[120]

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[109] L. Ruzicka and van Veen, *Ann.*, **468**, 133–143 (1929).
[110] L. Ruzicka and Hosking, *Helv. Chim. Acta*, **14**, 203 (1931).
[111] L. Ruzicka and Hosking, *Helv. Chim. Acta*, **13**, 1402 (1930).
[112] L. Ruzicka and Peyer, *Helv. Chim. Acta*, **18**, 676–684 (1935).

Hydrogenation effects can appear even in double bonds which are part of a six-membered ring in which dehydrogenation to a parent aromatic compound should be possible. An example of this is the formation of α-naphthylcyclohexane from α-naphthylcyclohexene, reported by Cook and Lawrence.[121] Such reactions are especially frequent in catalytic dehydrogenation, which often involves disproportionation rather than the complete removal of hydrogen.

VI. NORMAL DEHYDROGENATION

Normal dehydrogenations, those in which no cleavage, rearrangement, or formation of a carbon-to-carbon bond occurs, in general proceed readily and in good yield with all three of the common dehydrogenation methods, so that these processes can often be used in preparative work. The developments of the past few years have brought the catalytic method into considerable favor for the dehydrogenation of those compounds which contain no quaternary carbon atoms.

Developing the work of Sabatier[122] on the dehydrogenation of cyclohexane to benzene by the use of finely divided nickel, Zelinsky[17] observed that the platinum metals catalyze this reaction at considerably lower temperatures. Since under these mild reaction conditions some other hydrocarbons, such as cyclopentane derivatives, are not attacked, hydrocarbon mixtures can be separated by selective dehydrogenation.[123] This method was applied to the investigation of the "naphthenes" of petroleum[124,125] and to the determination of cyclopentanes in paraffin hydrocarbons.[126]

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[113] Dorée and Petrov, *J. Chem. Soc.*, **1934**, 1129–1130.

[114] Dorée and Petrov, *J. Chem. Soc.*, **1935**, 1391–1393.

[115] Zelinsky and Titz, *Ber.*, **62 B**, 2869–2873 (1929).

[116] Levina and Trakhtenberg, *J. Gen. Chem.* (*U. S. S. R.*), **6**, 764–773 (1936).

[117] Levina and Tzurikov, *J. Gen. Chem.* (*U. S. S. R.*), **4**, 1250–1257 (1934).

[118] Cohen, J. W. Cook, and Hewett, *J. Chem. Soc.*, **1935**, 1633–1637.

[119] J. W. Cook and Haslewood, *J. Chem. Soc.*, **1935**, 767–770.

[120] Yokoyama and Kotake, *Bull. Chem. Soc. Japan*, **10**, 138 (1935); also in *J. Chem. Soc. Japan*, **56**, 336–337 (1935).

[121] J. W. Cook and Lawrence, *J. Chem. Soc.*, **1936**, 1431–1434.

[122] Sabatier, *Ber.*, **44**, 1984 (1911).

A large number of substituted cyclohexanes, hydrogenated naphthalenes and phenanthrenes, and hydrogenated derivatives of higher condensed aromatic systems can be readily dehydrogenated to their parent aromatic compounds. Examples are the dehydrogenation of menthane,[127] hexahydrozingiberene,[108] decalin,[125,128,129] 2-benzyldecalin,[130] hydrindane,[115] hexahydrofluorene,[130] and octahydroanthracene.[131] With the higher boiling compounds dehydrogenation in the vapor phase, which is somewhat inconvenient from the standpoint of the apparatus involved, can be replaced by simple heating under reflux in the presence of the catalyst. However, care must always be taken that the dehydrogenation mixture really attains the required temperature, which in certain cases can be as high as 350°C.

The behavior of tetralin, octalin, decalin, octahydroanthracene, and octahydrophenanthrene toward platinum and palladium catalysts has been very thoroughly investigated by Linstead and co-workers.[64,129,132] According to their results, tetralin is rapidly dehydrogenated in the liquid phase even at a temperature of 185°C. when vigorous boiling is insured, by the application of a slight vacuum for example; decalin, on the other hand, requires a temperature of about 300°C. Octalin undergoes disproportionation to tetralin and decalin before dehydrogenation. The catalytic dehydrogenation of limonene proceeds in a similar manner[65]; it is disproportionated to menthane and cymene by heating in the presence of the catalyst, even at 140°C. Complete dehydrogenation occurs only at about 305°C. The same is true of cadinene.

Even though, because of their simplicity and cleanliness, the catalytic methods really give the best results for such dehydrogenations, sulfur and selenium have also frequently been used. In general, both of these reagents give good results for the dehydrogenation of partially unsaturated compounds, as is apparent from the work of Ruzicka, Haworth, Cook, and others. Perhydro compounds, however, resist dehydrogenation by these chemical methods, even at temperatures above 350°C. The fact that tetrahydrocadinene, in contrast to cadinene itself, is not dehydrogenated by sulfur at 200° to 260°C. was established very early.[3] It is interesting to note, however, that the perhydroazulenes can be dehydrogenated by sulfur and selenium.[133] *trans*-Decalin is only slightly attacked by selenium in the sealed tube at 350°C.,[134] and 2-methyldecalin at 320° to 350°C gives only a very small yield of dehydrogenation product.[135] This extraordinary resistance of perhydrogenated compounds to the chemical methods of dehydrogenation is probably related to the mechanism of the reactions.

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[123] Zelinsky, *Ber.*, **45,** 3678–3682 (1912).

[124] Zelinsky, *Ber.*, **56,** 1718–1723 (1923).

[125] Kaffer, *Ber.*, **57 B,** 1261 (1924).

[126] Turova-Pollak, Zelinsky, and Gasan-Zade, *Compt. rend. acad. sci. U. R. S. S.*, **32,** 551–554 (1941).

[127] Zelinsky, *Ber.*, **56,** 787–788 (1923).

[128] Zelinsky, *Ber.*, **56,** 1723–1724 (1923).

[129] Linstead, Millidge, Thomas, and Walpole, *J. Chem. Soc.*, **1937,** 1146–1157.

[130] J. W. Cook and Hewett, *J. Chem. Soc.*, **1936,** 62–71.

[131] Maillard, *Compt. rend.*, **200,** 1856–1858 (1935).

[132] Linstead and Thomas, *J. Chem. Soc.* **1940,** 1127–1134.

VII. DEHYDROGENATION ACCOMPANIED BY CHANGE IN CARBON SKELETON

The behavior of *quaternary methyl groups* during dehydrogenation has been studied in detail, and is of decided interest, since a large number of natural products contain groups of this type. The fact that certain methyl groups can be eliminated by dehydrogenation was definitely established for the first time by Ruzicka and co-workers,[3,6,7] who noted that sulfur dehydrogenation of the sesquiterpenes of the eudasmol series yielded eudalene. To explain this, it was pointed out that the position occupied in the original hydrogenated ring system by the methyl group does not exist in the corresponding aromatic structure. The methyl group is therefore split out, since it is a hindrance to the dehydrogenation. This assumption has subsequently been proved valid. The important point in this connection is that the quaternary group is almost always completely eliminated from the molecule, only in a few definite cases migrating to a neighboring carbon atom. This rule has been derived from the dehydrogenation results of a large number of natural products, particularly the sterols. Because of its importance, this regularity of behavior has also been thoroughly investigated with synthetic compounds. Ionene, for example, which contains two geminal methyl groups, gives 1,6-dimethylnaphthalene on dehydrogenation with sulfur or selenium.[15,136] Similar results have been obtained from a number of other experiments, particularly those by Cook[92,121,137,138] and Linstead.[139,140]

The work of Zelinsky[141–143] gave some support to the original supposition that catalytic dehydrogenation is completely inhibited by the presence of quaternary methyl groups. More recent data do not confirm this opinion, but catalytic dehydrogenation does differ fairly markedly from the chemical methods in this respect.

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[133] L. Ruzicka and Haagen-Smit, *Helv. Chim. Acta*, **14**, 1104–1122 (1931).
[134] L. Ruzicka and Seidel, *Helv. Chim. Acta*, **19**, 424–433 (1936).
[135] Barret, A. H. Cook, and Linstead, *J. Chem. Soc.*, **1935**, 1065–1069.
[136] Clemo and Dickenson, *J. Chem. Soc.*, **1935**, 735–738.
[137] J. W. Cook and Girard, *Nature*, **133**, 377–378 (1934).
[138] Bachmann, J. W. Cook, Hewett, and Iball, *J. Chem. Soc.*, **1936**, 54–61.
[139] Hibbit and Linstead, *J. Chem. Soc.*, **1936**, 470–476.
[140] Errington and Linstead, *J. Chem. Soc.*, **1938**, 666–672.
[141] Zelinsky and Shuikin, *Ber.*, **62 B**, 2180–2186 (1929).
[142] Zelinsky, *Ber.*, **56**, 1716–1718 (1923).
[143] Zelinsky, Packendorff, and Khokhlova, *Ber.*, **68 B**, 98–101 (1935).

Ruzicka and Waldmann[144] pointed out some time ago that retene is formed in excellent yield (85%) from both abietic acid and fichtelite[145] with palladium-charcoal. In both cases the gases evolved contain large amounts of methane. These results indicate that quaternary groups are no intrinsic hindrance to catalytic dehydrogenation.

The influence of quaternary groups on catalytic dehydrogenation was recently carefully studied by Linstead and co-workers.[65,129,132] Octalins without quaternary methyl groups are rapidly disproportionated at the boiling point to tetralin and decalin, following which the tetralin is further dehydrogenated; the dehydrogenation of the completely saturated decalin, however, proceeds very slowly under these conditions. In the case of octalins substituted in the 9 position, the disproportionation is hindered; so these compounds are dehydrogenated only at higher temperatures, as high as those required for even the completely saturated decalins to react with a practical velocity (about 330°C.). No real difference seems to exist, however, between the dehydrogenation temperatures of decalins with or without quaternary methyl groups; the dehydrogenation of 9-methyldecalin proceeds somewhat more slowly and in somewhat poorer yield than does that of the unsubstituted compound.[129]

It is of interest to note, however, that both decalin and 9-methyldecalin are dehydrogenated at lower temperature by the catalytic methods than by the use of selenium.

Selinene, which also contains a quaternary methyl group, is converted about one-third to eudalene, in addition to tetrahydroselinene, at a temperature as low as 205°C., but in a relatively slow reaction.[65] This is probably the first reported example of the splitting out of an angular methyl group by catalytic dehydrogenation at so low a temperature.

In contrast to the catalytic methods,the temperatures necessary for dehydrogenation by sulfur and selenium are increased only slightly by the presence of quaternary methyl groups. For example, ionene,[15] the sesquiterpenes of the eudasmol group,[3] and similar compounds have been dehydrogenated with sulfur at temperatures not greatly in excess of those required for the dehydrogenation of the cadalene derivatives.[3] The yields of aromatic hydrocarbons were, to be sure, considerably lower in most cases, about 10% with ionene and eudasmol in contrast to 50 to 60% with cadinene. Similar yields have also been obtained by dehydrogenation with selenium.[146] Perhydro compounds, however, usually differ from these partially unsaturated compounds; they are dehydrogenated with selenium only at temperatures above 350°C., whether they contain quaternary methyl groups or not. For example, cholestane,[130] perhydro-vitamin D_2,[130] and other completely saturated compounds[136,147,148] are dehydrogenated only incompletely or not at all with selenium at temperatures up to 350°C. The failure of 1,1-dimethyltetralin to dehydrogenate with sulfur, and of 2,2-dimethyl- or 2,2-diethyltetralin with selenium,[149,150] by heating under atmospheric pressure, can probably be attributed to the low boiling points of these compounds, since 2,2-dimethyltetrahydrophenanthrene readily gives 2-methylphenanthrene by reaction with selenium at 300° to 340°C.; also the dehydrogenation of the above tetralins can be readily accomplished at a temperature as low as 320°C. in the sealed tube.[149,151] According to Barker and Clemo,[152] 2-methylphenanthrene is obtained from 2-methyl-2-ethyl-1,2,3,4-tetrahydrophenanthrene by heating with selenium at 280° to 300°C. for 24 hours.

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[144] L. Ruzicka and H. Waldmann, *Helv. Chim. Acta*, **16**, 842 (1933).
[145] L. Ruzicka and E. Waldmann, *Helv. Chim. Acta*, **18**, 611–612 (1935).

In the researches mentioned above,[129,132] Linstead and co-workers made several fundamental new observations on the behavior of quaternary methyl groups during catalytic dehydrogenation. By the action of the majority of the platinum and palladium catalysts investigated, the angular methyl group of 9-methyldecalin is almost completely eliminated to form naphthalene, but small amounts of α-methylnaphthalene are always formed as a by-product. This migration seems to occur especially with platinum and palladium catalysts precipitated on asbestos. Attempts to investigate the mechanism of these reactions by means of experiments on dimethylated decalins and octalins have not yet yielded conclusive results.[132] A similar migration also occurs in traces during the dehydrogenation of 1,1-dimethylnaphthalene, which gives some 1,2-dimethylnaphthalene in addition to 1-methylnaphthalene.

Aside from those cases which can be interpreted as retropinacoline rearrangements (see p. 26), this migration is probably the first definitely established exception to the rule that quaternary methyl groups are always completely eliminated. If it were possible to generalize the conditions necessary for migration, a means would be provided of fixing the position of quaternary groups, with the help of specific catalysts which promote migration. Linstead and co-workers have reported on a similar but fruitless research on selinene.[65]

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[146] Diels and Karstens, *Ber.*, **60 B**, 2323–2325 (1927).

[147] C. K. Chuang, Y.-L. Tien, and C. M. Ma, *Ber.*, **69 B**, 1494–1505 (1936).

[148] Clemo and Haworth, *J. Chem. Soc.*, **1930**, 2579.

[149] Sen-Gupta, *Science and Culture*, **2**, 589 (1937); *Chem. Zentr.*, **1937, II**, 2165.

[150] Clemo and Dickenson, *J. Chem. Soc.*, **1937**, 255–257. Bogert, Davidson, and Apfelbaum, *J. Am. Chem. Soc.*, **56**, 959 (1934).

[151] Sen-Gupta, *J. prakt. Chem.*, **151**, 82–96 (1938).

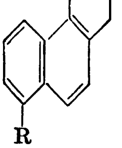
[152] Barker and Clemo, *J. Chem. Soc.*, **1940**, 1277–1279.

The fact that no groups but quaternary methyl groups are split out or migrate during dehydrogenation is of absolutely fundamental importance in applying the method to the determination of constitution. This principle has been confirmed by experiment in the great majority of cases. Certain exceptions recorded in the literature are discussed below.

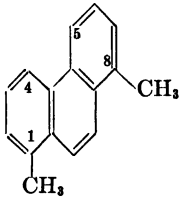
MIGRATION OF SIDE CHAINS. Mayer and Schiffner[153] have pointed out that α-alkylnaphthalenes are converted into β-alkylnaphthalenes in the presence of silica gel at about 420°C. In the case of α-phenylnaphthalene this migration occurs even at 350°C. Such rearrangements, which are independent of true dehydrogenation processes, might possibly be promoted by the material of the reaction vessel or by the catalyst carrier, effects which have occasionally been noticed during dehydrogenation. According to the results published so far, an α-β migration in naphthalene derivatives evidently does not occur during selenium dehydrogenation at temperatures below 350°C. Since for structural reasons this type of migration can take place only in one direction, it would be very worth while to have accurate data on the thermal stability of alkyl derivatives of phenanthrene, chrysene, picene, and the other aromatic hydrocarbons which commonly form the nuclei of dehydrogenation products.

This problem came up especially in connection with the rearrangements observed during the dehydrogenation of various phenanthrene derivatives.[154] For example, from the hydrocarbon XVI with selenium there were obtained mainly 1,8-dimethylphenanthrene (XVII) and only a small amount of the expected 1,5 isomer. In other cases, also, a migration of methyl groups from the 4 or 5 position to the 1 or 8 position, respectively, has occurred.

Neither 4- nor 1-methylphenanthrene could be isolated from the products of dehydrogenation of XVIII. In contrast to all these results, how-



(XVI) R = CH$_3$
(XVIII) R = H



(XVII)

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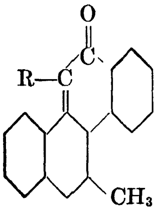
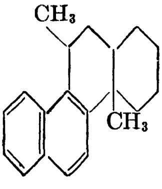
[153] Mayer and Schiffner, *Ber.*, **67 B**, 67–69 (1934).
[154] Haworth, Mavin, and Sheldrick, *J. Chem. Soc.*, **1934**, 454–461.

ever, Bachmann and Edgerton[155] were able to obtain 4-methylphenanthrene from XVIII by a very smooth reaction with palladium-charcoal at 300° to 320°C.; other phenanthrenes substituted in the 4 position are also readily prepared by dehydrogenation. Similar contradictions appear in the preparation of 1,4-dimethylphenanthrene[91,156,157] and of 4-methylphenanthrene,[77,158–160] in which, according to the method employed, different products are obtained.

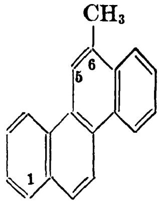
Unexpected results have also been obtained in the chrysene series at various times. Thus, in the dehydrogenation of the ketone XIX (R = CH_3) and of the ketone XIX (R = H) with selenium, chrysene was the main product, along with small amounts of a monomethylchrysene.[161] Fieser and co-workers[162] obtained 6-methylchrysene in low yield from XX with selenium, instead of the expected 5 isomer.



(XIX)



(XX)



(XXI)

However, Newman[163–165] was able to prepare methylchrysene by a different method, which also employed a dehydrogenation as the final step. This, however, was achieved with sulfur at the comparatively low temperature of 250°C. Attempts have been made to explain the anomalous results as due to steric hindrance. The work on this phase of the question will not be discussed in any detail, but it may be mentioned that even 4,5-dimethylchrysene can be obtained as a reaction product by careful dehydrogenation with sulfur, without any indication of rearrangement or splitting off of methyl groups, although the yield is poor.[166] It is still very questionable, therefore, whether the rearrangements which have been noticed in monomethyl derivatives really occur during the dehydrogenation. This entire complex question still needs considerable study.

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[155] Bachmann and Edgerton, *J. Am. Chem. Soc.*, **62**, 2219–2223 (1940).

[156] Akin, Stamatoff, and Bogert, *J. Am. Chem. Soc.*, **59**, 1268–1272 (1937).

[157] Papa, Perlmann, and Bogert, *J. Am. Chem. Soc.*, **60**, 319–321 (1938).

[158] Radcliffe, Sherwood, and Short, *J. Chem. Soc.*, **1931**, 2293–2297.

[159] Haworth, *J. Chem. Soc.*, **1932**, 1125.

[160] Darzens and A. Lévy, *Compt. rend.*, **201**, 730–733 (1935).

[161] Jones and Ramadge, *J. Chem. Soc.*, **1938**, 1853–1858.

[162] L. F. Fieser, Joshel, and Seligman, *J. Am. Chem. Soc.*, **61**, 2134–2139 (1939).

[163] Newman, *J. Am. Chem. Soc.*, **62**, 870–874 (1940).

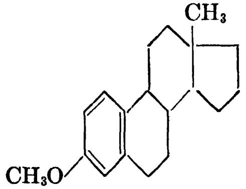
[164] See also L.F. Fieser and Joshel, *J. Am. Chem. Soc.*, **62**, 1211–1214 (1940).

[165] See also Bachmann and Edgerton, *J. Am. Chem. Soc.*, **62**, 2550–2553 (1940).

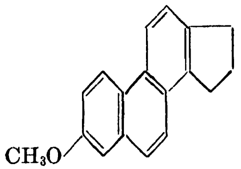
[166] Newman. *J. Am. Chem. Soc.*. **62**, 2295–2300 (1940).

Other rearrangements of methyl groups, such as that observed in the decomposition of alantolactone,[167] probably result from the thermal effects which precede and are independent of the dehydrogenation.

These isolated cases, for which the mechanism is still not completely understood, are quite different from migrations of alkyl groups which have the character of a retropinacoline rearrangement and which have already been mentioned (p. 26) in connection with the discussion of the behavior of secondary hydroxyl groups. The same type of rearrangement of quaternary methyl groups also occurs when other adjacent groups, such as long side chains, are eliminated. The best known and most accurately investigated example of this is the formation of γ-methylcyclopentenophenanthrene by the dehydrogenation of the sterols. In this case, certainly, the isooctyl side chain in first split off (an example of the thermal decomposition, independent of the dehydrogenation, which was observed some time ago[168]), after which the methyl group in position 13 migrates to position 17 and thereby makes possible the dehydrogenation of Ring C.[169–172] This reaction mechanism is also supported by the fact that the compound XXII is converted into XXIII by dehydrogenation with selenium, with the elimination (not migration!) of the methyl group.[137] (See also the dehydrogenation of 8-methylhexahydroindane to indane.[140])



(XXII)



(XXIII)

Elimination of Side Chains. There appear to be no well established examples of the elimination of non-quaternary methyl groups. A somewhat similar reaction, the simultaneous elimination of two geminal methyl groups, may have occurred in traces during the dehydrogenation of 1,1-dimethyltetralin with very active catalysts,[132] but the behavior of longer non-quaternary side chains has not yet been worked out. It is very probable that long side chains can be retained in the molecule by careful dehydrogenation at moderate temperatures.

A number of dehydrogenation products have been reported which contain isopropyl, *n*-propyl, *t*-butyl,[66] and even heavier side chains.[130] For example, β-phenylethylnaphthalene can be prepared from β-phenylethyloctalin.[173] On the other hand, there are numerous cases of the cleavage of such side chains, particularly at the relatively high temperatures of selenium dehydrogenation. This is the case, for example, in the dehydrogenation of the maleic anhydride adduct of vitamin D_2 (XII), which forms 2,3-dimethylnaphthalene with selenium, and β-naphthoic acid and naphthalene with palladium-charcoal; the side chain with Rings C and D is therefore completely eliminated.[106] The splitting off of butyric acid from XXIV with the formation of α-naphthol has also been reported.[174] A similar observation was made by Bergmann.[175] However, with selenium at 390° to 400°C., 1,1,3-trimethyl-2-*n*-butylcyclohexane (XXV) gives a mixture of *m*-xylene and 1,3-dimethyl-2-*n*-butylbenzene.[134] The reaction involves in part, therefore, the complete elimination of the butyl side chain, without a simultaneous migration of the quaternary methyl groups resulting. Dehydrogenation of the dimeric cyclohexadiene (XXVI) gives naphthalene.[176] In this case the thermal splitting off of ethylene is to be expected on the basis of other experiments; similar results were obtained with various derivatives of bicyclo[2.2.2]octane.[177] The splitting off of isopropyl groups, probably in the form of isopropylene, has also been observed.[51,65] It has been suggested[178] that the presence of 1,6-dimethylnaphthalene in the product obtained from the selenium dehydrogenation of isozingiberene may be due to the cleavage of the isopropyl group of cadalene, the initial product of the reaction.

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[167] L. Ruzicka, Pieth, Reichstein, and Ehmann, *Helv. Chim. Acta*, **16**, 268 (1933).

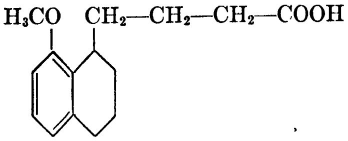
[168] Fischer and Treibs, *Ann.*, **446**, 241 (1925).

[169] J. W. Cook, *Chemistry and Industry*, **54**, 176 (1935).

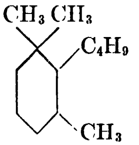
[170] Bergmann, *Chemistry and Industry*, **54**, 175–176 (1935).

[171] Rosenheim and King, *Chemistry and Industry*, **52**, 299–301 (1933).

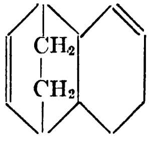
[172] Cohen, J. W. Cook, and Hewett, *J. Chem. Soc.*, **1935**, 445–455.



(XXIV)



(XXV)



(XXVI)

In all of the above examples, existing side chains are completely split out. In other cases, dehydrogenation reactions have been interpreted as taking place with only a partial elimination of the side chain, so that a methyl group is left behind. According to this, the formation of agathalene (XXVII) from agathenedicarboxylic acid (XXVIII) would be explained by fission at *a*[110]; and thus the methyl group in the 5 position of the agathalene molecule would be indicated as the place of attachment of the C_6 side chain. Except in the case of sclareol,[179,180] a similar reaction mechanism has been adopted to explain the formation of the various methylated naphthalenes by the dehydrogenation of the pentacyclic triterpenes, in which case the breaking apart of the molecule at Ring C can be formally compared with the splitting off of side chains. (See Formula I, fission according to *a*; for corresponding formulations see the literature.[43,47,49,181])

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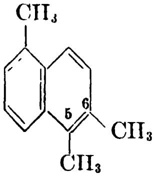
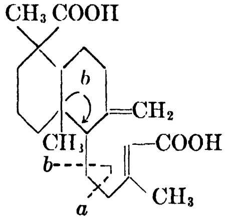
[173] J. W. Cook and Hewett, *J. Chem. Soc.*, **1934**, 365–377.
[174] L. F. Fieser and Hershberg, *J. Am. Chem. Soc.*, **58**, 2382–2385 (1936).
[175] Bergmann, *J. Am. Chem. Soc.*, **60**, 1798–1799 (1938).
[176] F. Hofmann, *Chem.-Ztg.*, **57**, 5–6 (1933).
[177] Kasansky and Plate, *Ber.*, **68 B**, 1259–1264 (1935).
[178] Seidel, Müller, and Schinz, *Helv. Chim. Acta*, **27**, 738–747 (1944).

In a number of instances, however, the results can be explained just as well by assuming complete splitting out of the longer side chain or of the corresponding rings, with simultaneous migration of a neighboring quaternary methyl group (*e.g.*, scheme *b*, Formula XXVIII). This reaction is known from sterol chemistry (see the preceding section).



(XXVII)



(XXVIII)

Cleavage *a* with elimination of methyl group

Cleavage *b* with migration of methyl group

Since type experiments on synthetic materials containing long side chains are almost non-existent at the present time, it is impossible to decide which of these two mechanisms best describes the reaction, whether the side chains are preferentially eliminated completely or with the retention of a methyl group. It is possible that both processes can proceed simultaneously. A more accurate knowledge of this reaction mechanism would be valuable in interpreting the results of the dehydrogenation of many natural products. It would then perhaps be possible to obtain criteria for the presence of quaternary methyl groups, just as the formation of γ-methylcyclopentenophenanthrene points to the presence of a quaternary methyl group on C_{13}.

EXPANSION OF RINGS. Many of the familiar ring expansions can be formulated in a manner formally analogous to the migration of alkyl groups. The dehydrogenation results obtained with spiro compounds, especially, frequently have the nature of retropinacoline rearrangements. This applies, for example, to the formation of naphthalene from cyclopentanespirocyclohexanone.[182] Of course, the dehydrogenation of hydrocarbons, such as

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[179] L. Ruzicka and Janot, *Helv. Chim. Acta*, 14, 645 (1931).

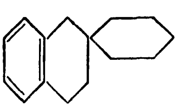
[180] L. Ruzicka, Engel, and Fischer, *Helv. Chim. Acta*, 21, 364–370 (1938).

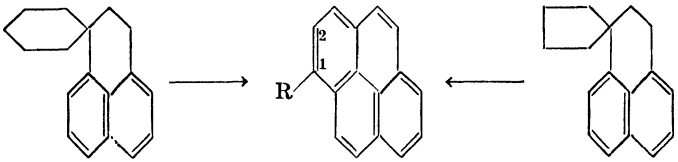
[181] L. Ruzicka, Furter, Pieth, and Schellenberg, *Helv. Chim. Acta*, 20, 1564–1570 (1937).

[182] Clemo and Ormston, *J. Chem. Soc.*, 1933, 352–353.

cyclopentanespirocyclohexane, cannot be formulated as retropinacoline rearrangement, but in some cases it is possible that a rearrangement of this type has occurred during the preparation of the hydrocarbon. The dehydrogenation of spiro compounds has been thoroughly treated by Chatterjee and co-workers,[183–185] in connection with synthetic work. According to Sen-Gupta, a small amount of anthracene is formed, in addition to a large quantity of phenanthrene, by the dehydrogenation of 1,2,3,4-tetrahydronaphthalene-3,1′-spirocyclopentane with selenium at 300° to 350°C.[186] This indicates that the reaction involves cleavage of a quaternary bond and ring closure of the resulting side chain.[187] This reaction takes place at a remarkably low temperature.

Sen-Gupta has reported also that 1,2,3,4-tetrahydronaphthalene-2,1′-spirocyclohexane (XXIX) is converted to phenanthrene by selenium dehydrogenation, with the loss of 1 carbon atom.[188,189] Similarly, 7-methyl- and 7-ethyl-1,2,3,4-tetrahydronaphthalene-2,1′-spirocyclohexane give 3-methyl- and 3-ethylphenanthrene, respectively.[189] According to Cook and Hewett,[173] pyrene (XXX, R = H) is obtained from XXXI by a similar reaction, with the loss of 2 carbon atoms, while XXXII gives 1-methylpyrene (XXX, R = CH_3).


(XXIX)



(XXXI) (XXX) (XXXII)

Catalytic dehydrogenation, also, can convert spiro compounds into fully condensed aromatic ring systems. Levitz and Bogert[190] obtained 9-methylphenanthrene from 4-methyl-1,2,3,4-tetrahydronaphthalene-1,1′-spirocyclopentane by heating with palladium-charcoal at 330° to 340°C. for 5 hours. Marvel and Brooks[191] converted spirodecane and 3-methylspirodecane to naphthalene and 1-methylnaphthalene, respectively, with either palladium- or platinum-charcoal at a temperature of 325°C. Surprisingly, selenium at 330° to 350°C. did not dehydrogenate these spiranes, the starting material being recovered unchanged.

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[183] Chatterjee, *J. Indian Chem. Soc.*, **14**, 259–263 (1937).
[184] Chatterjee, *J. Indian Chem. Soc.*, **13**, 536–541 (1936).
[185] Chatterjee, *J. Indian Chem. Soc.*, **13**, 588–592 (1936).
[186] Sen-Gupta, *J. Indian Chem. Soc.*, **11**, 389–394 (1934).
[187] See L. Ruzicka and Waldmann, *Helv. Chim. Acta*, **16**, 843, note 2 (1933).
[188] S. C. Sen-Gupta, *Science and Culture*, **3**, 57 (1937).
[189] S. C. Sen-Gupta, *J. Indian Chem. Soc.*, **19**, 467–472 (1942).
[190] Levitz and Bogert, *J. Org. Chem.*, **8**, 253–255 (1943).
[191] Marvel and Brooks, *J. Am. Chem. Soc.*, **63**, 2630–2632 (1941).

Other work has been reported, however, in which spiranes have not undergone rearrangement and consequently have not been aromatized by dehydrogenation.[91,92,118,192,193] No definite rules can be derived from the data published so far. Spiro compounds appear to be unaffected, particularly, by careful catalytic dehydrogenation[141] and thus can be separated from isomers which are more readily attacked.

The ring enlargement to chrysene which results during the dehydrogenation of the sterols has been of great importance in determining the constitution of these compounds. This enlargement was first noticed by Diels and co-workers[194,195] during the dehydrogenation of cholesterol with palladium-charcoal and of cholic acid with selenium.[196] Exhaustive experiments showed that this type of ring enlargement occurred only at temperatures above 400°C.[197,198] Inasmuch as γ-methylcyclopentenophenanthrene[197] could not be definitely detected in the product when chrysene was present, it is probably safe to assume that the chrysene is formed from the γ-methylcyclopentenophenanthrene as a result of the high dehydrogenation temperature. Although it has not yet been possible to duplicate this reaction experimentally, somewhat similar experiments by Ruzicka and Peyer[112] have nevertheless led to interesting results. α-Methylindane gives a good yield of naphthalene, both with selenium and with palladium-charcoal, at about 450°C. Naphthalene is also formed from β-methyl-, from α- and β-ethyl-, and even from isooctylindane under these conditions. This investigation has shown that the dehydrogenation temperatures should not be permitted to go much above 350°C. if these secondary reactions are not desired. In general, such reactions could not be detected at temperatures below 350°C.[199]

CONTRACTION OF RINGS. At temperatures of about 400°C., cycloheptane and cyclooctane derivatives undergo contraction of the ring. The conditions necessary for this reaction have been thoroughly investigated by experiments on type materials, especially by Ruzicka and Seidel.[134] Cycloheptane was converted to toluene by treatment with selenium at 440°C., and cyclooctane to p-xylene at 390° to 410°C. Alkyl derivatives of these hydrocarbons and cyclopentadecane were also studied. A uniform reaction scheme could not be set up; however, the cycloheptane ring is aromatized with selenium even under conditions not much more vigorous than those

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[192] Bogert, *Science*, **84**, 44–45 (1936).

[193] Perlmann, Davidson, and Bogert, *J. Org. Chem.*, **1**, 300–304 (1936).

[194] Diels and Gädke, *Ber.*, **58 B**, 1231 (1925).

[195] Diels and Gädke, *Ber.*, **60 B**, 140–147 (1927).

[196] Diels and Karstens, *Ann.*, **478**, 129 (1930).

[197] L. Ruzicka, Thomann, Brandenberg, Furter, and Goldberg, *Helv. Chim. Acta*, **17**, 200–221 (1934).

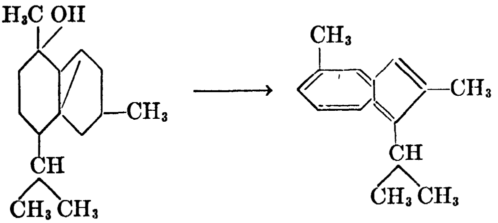
[198] L. Ruzicka and Goldberg, *Helv. Chim. Acta*, **20**, 1245–1253 (1937).

[199] See, however, Nenitzescu and Cioranescu, *Ber.*, **69 B**, 1040–1041 (1936).

necessary for the conversion of decalin to naphthalene. Ruzicka and Seidel[134] also briefly discuss earlier experiments by Zelinsky and co-workers.[123]

The catalytic dehydrogenation and isomerization of methylcycloheptane with platinized carbon at 305° to 310°C. is reported by Turova-Pollak and Rappoport.[200] In six passes over the catalyst, a 94% yield is obtained of an aromatic product consisting mainly of *p*-xylene, with traces of the meta isomer.

Cleavage of Rings. In addition to ring enlargements and ring contractions, the cleavage of rings and the formation of new rings are also frequently observed during dehydrogenation. The cleavage of three-membered rings in polycyclic systems occurs very readily when the dehydrogenation to aromatic products is made possible by that means. One example of this which has been known for a long time is the formation of cadalene from the tricyclic sesquiterpene copaene,[201] which is readily converted even by treatment with hydrochloric acid into the bicyclic cadinene dihydrochloride.



(XXXIII) (XXXIV)

More recently, the analogous formation of azulenes from tricyclic sesquiterpenes has been observed. Komppa[202] found that both cadalene and an azulene result from ledol or ledene on dehydrogenation. This reaction has been formulated, as shown in Formulas XXXIII and XXXIV, by Komppa and Nyman.[203]

According to Radcliffe and Short,[204] the formation of guaiazulene from aromadendrene may proceed in an analogous manner. It is surprising that in these cases the ring disintegration which produces azulenes appears to take preference over the equally possible formation of naphthalenes. The primary process in these reactions is probably the thermal cleavage of a ring structure, resulting in the formation of unsaturated derivatives. If these have a suitable structure, they are then dehydrogenated. Aside from the cases just mentioned, however, such phenomena are very rare in dehydrogenations with sulfur and selenium. The tricyclic sesquiterpenes, for example, in general give either none at all or only traces of aromatic dehydrogenation products.[1,205]

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[200] Turova-Pollak and Rappoport, *J. Gen. Chem.* (*U. S. S. R.*), **13**, 353–357 (1943).

[201] Henderson, McNab, and Robertson, *J. Chem. Soc.*, **1926**, 3077.

[202] Komppa, *Kgl. Norske Videnskab. Selskabs, Skrifter*, **1933**, No. 1, 16 pp.; *Chem. Abstracts*, **28**, 4724 (1934).

[203] Komppa and Nyman, *Compt. rend. trav. lab. Carlsberg, Sér. chim.*, **22**, 272–274 (1938); *Chem. Abstracts*, **32**, 6234 (1938).

[204] Radcliffe and Short, *J. Chem. Soc.*, **1938**, 1200–1203.

The use of catalytic dehydrogenation, on the other hand, enabled Zelinsky and co-workers to conduct a thorough investigation into the behavior of various ring systems. Their first experiments show that five membered rings are not attacked by metallic catalysts. Certain exceptions, such as cyclohexylmethylcyclopentane[206] and dicyclopentyl,[207] which yield diphenyl and naphthalene, respectively, could be ascribed to the fact that the hydrogenated hydrocarbons are well suited to become the carbon skeleton of the dehydrogenation product.[207,208] Catalytic dehydrogenation therefore gives consistent results and has been very valuable in explaining the rearrangements which take place during the preparation of the hydrogenated compounds.

In the course of such investigations, the dehydrogenation of a number of members of a series of bicyclic systems, such as bicyclo[1.2.2]heptanes,[209] bicyclo[2.2.2]octanes,[176,177] bicyclo[0.3.3]octanes,[210] and bicyclo[1.3.3]-nonanes,[130] has been studied. Of these compounds, the bicyclo[2.2.2]octanes are dehydrogenated relatively easily, since they can decompose into a cyclohexane and an ethylene derivative in accordance with a familiar reaction.[211,212]

Elagina and Zelinsky[213] dehydrogenated 2,3-benzobicyclo[3.3.1]-2-nonene over platinized charcoal at 300°C. With a moderately active catalyst, diphenylmethane is the main product; with a more active platinized charcoal, increasing amounts of fluorene are found in the product.

The catalytic dehydrogenation of bicyclic terpenes of the carane, pinane, and thujane types has also been investigated.[65,214-216] In some cases *p*-cymene was obtained. In others, breaking up of one of the rings occurred, with the formation of cyclopentane derivatives which resisted further dehydrogenation.

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[205] L. Ruzicka and Stoll, *Helv. Chim. Acta*, **6**, 846 (1923).
[206] Zelinsky, *Ber.*, **58 B**, 2755–2763 (1925).
[207] Zelinsky, Titz, and Fataiev, *Ber.*, **59 B**, 2580 (1926).
[208] Zelinsky and Titz, *Ber.*, **64 B**, 183–188 (1931).
[209] Zelinsky, Kasansky, and Plate, *Ber.*, **66 B**, 1415 (1933).
[210] Barrett and Linstead, *J. Chem. Soc.*, **1936**, 611–616.
[211] Diels, Alder, and Stein, *Ber.*, **62 B**, 2337–2372 (1929).
[212] Alder and Rickert, *Ann.*, **524**, 180–189 (1936); *Ber.*, **70 B**, 1354–1363, 1364–1369 (1937).
[213] Elagina and Zelinsky, *Compt. rend. acad. sci. U. R. S. S.*, **30**, 726–727 (1941).
[214] Zelinsky and Levina, *Ann.*, **476**, 60–70 (1929).
[215] Zelinsky and Kasansky, *Ber.*, **60 B**, 1096–1100 (1927).
[216] Zelinsky, *Ber.*, **58 B**, 864–869 (1925).

The passivity of cyclopentane derivatives[210,217,218] has been quite generally confirmed, but further research has shown that they are not completely resistant. Cyclopentane itself, for example, is hydrogenated to *n*-pentane in a hydrogen atmosphere over platinized charcoal even at 300°C.;[209] other compounds behave similarly.[219–222]

Under certain conditions, these aliphatic compounds can be again cyclicized to cyclohexane derivatives, which in turn can be dehydrogenated.[223] This reaction mechanism is supported by the fact that under similar conditions aliphatic compounds also yield small amounts of aromatic dehydrogenation products. For example, *p*-xylene is formed from diisobutyl, and *m*-cymene from diisoamyl.[223,224]

These observations detract little from the diagnostic value of catalytic dehydrogenation, however, since there is a marked difference between normal dehydrogenations and the phenomena described above, especially in the yields.

Formation of New Rings. The formation of new rings by the dehydrogenation reactions mentioned above is not unique. In addition to the conversion of the monocyclic zingiberene into a naphthalene derivative, numerous ring closures have been observed in dehydrogenations by both the chemical and the catalytic methods. Examples of these are the formation of fluorene from dicyclohexylmethane,[213,225,226] from diphenylmethane,[213,225,226] and from benzophenone, the formation of phenanthrene from cyclohexylcycloheptylmethane,[227] from diphenylethane,[116,225] and from stilbene.[116,225] This last reaction, according to Dewar and Read,[228] can be accomplished only with a palladium-charcoal catalyst prepared by Zelinsky's procedure; other platinum- and palladium-charcoals produce no cyclization. Berger obtained phenanthrene from di-*o*-tolyl with sulfur, at temperatures as low as 250°C.[229]; selenium did not cause ring formation. On the other hand, it has been reported elsewhere[76] that by the use of 2 moles of sulfur at 180° to 250°C. the compound XXXV is converted smoothly to di-*o*-tolyl, which gives phenanthrene only by distilling in the

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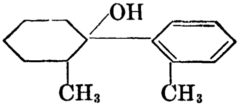
[217] Zelinsky, Mikhlina, and Eventova, *Ber.*, **66 B**, 1422 (1933).
[218] Denisenko, *Ber.*, **69 B**, 2183–2187 (1936).
[219] Zelinsky, Kasansky, and Plate, *Ber.*, **68 B**, 1869–1872 (1935).
[220] Zelinsky and Shuikin, *Compt. rend. acad. sci. U. R. S. S.*, **3**, 255–257 (1934).
[221] Denisenko, *Ber.*, **69 B**, 1668–1670 (1936).
[222] Zelinsky and Shakhnazarova, *Bull. acad. sci. U. R. S. S., Classe sci. math. nat., Sér. chim.*, **1936**, 571–574; *Chem. Abstracts*, **31**, 6621 (1937).
[223] Kasansky and Plate, *Ber.*, **69 B**, 1862–1869 (1936).
[224] Kasansky and Plate, *J. Gen. Chem.* (*U. S. S. R.*), **9**, 496–502 (1939).
[225] Zelinsky, Titz, and Gaverdovskaia, *Ber.*, **59 B**, 2590 (1926).
[226] See also Zelinsky and Gaverdovskaia, *Ber.*, **61 B**, 1049–1053 (1928).
[227] Elagina and Zelinsky, *Compt. rend. acad. sci. U. R. S. S.*, **30**, 728–731 (1941).
[228] Dewar and Read, *J. Soc. Chem. Ind.*, **55**, 347–349T (1936).
[229] Berger, *J. prakt. Chem.*, **133**, 331 (1932).

presence of sulfur. In further contrast to these results, Orchin obtained 4-methylfluorene from di-*o*-tolyl[230] and fluorene from 2-methyldiphenyl[231]

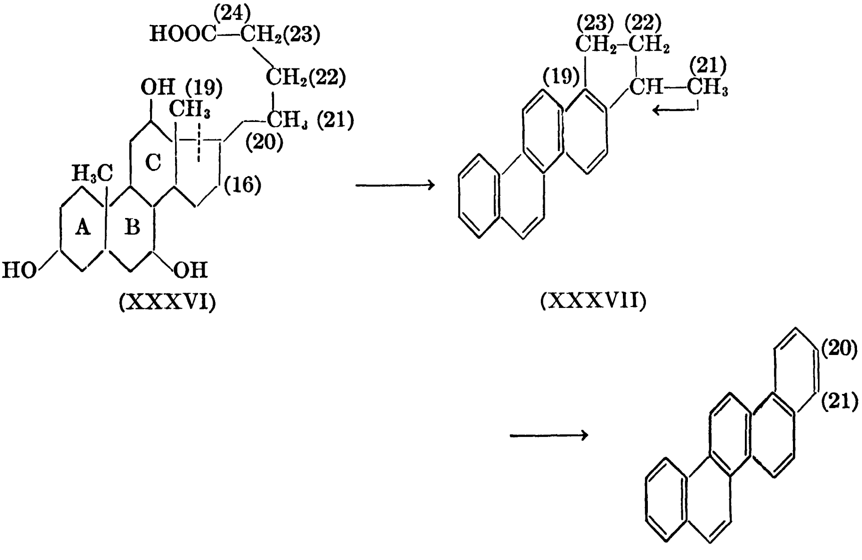


(XXXV)

by dehydrogenation with palladium-charcoal at 450°C. Naphthalene has been obtained from 1,2-diethyl-1-cyclohexene by the use of selenium under very vigorous conditions, heating in a sealed tube at 410° to 420°C.[112] Such side reactions can probably be prevented, however, by careful procedure.

Of a somewhat different type is the ring closure which took place during the dehydrogenation of vitamin A with selenium,[232] and which resulted in the formation of 1,6-dimethylnaphthalene.

In a similar manner, new rings are formed by the dehydrogenation of sterols and gallic acids. Ruzicka and co-workers obtained picene by the dehydrogenation of cholic acid or cholatrienic acid with selenium at 360°C.[40,233] This reaction has been explained according to Formulas XXXVI to XXXVIII.[197] Whether picene also results from the dehydro-



(XXXVI)

(XXXVII)

(XXXVIII)

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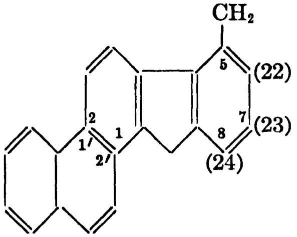
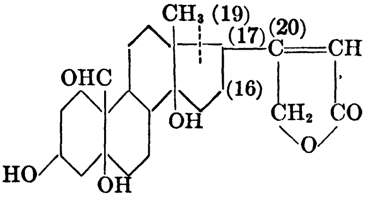
[230] Orchin and Woolfolk, *J. Am. Chem. Soc.*, **67**, 122–124 (1945).
[231] Orchin, *J. Am. Chem. Soc.*, **67**, 499 (1945).
[232] Heilbron, Morton, and Webster, *Biochem. J.*, **26**, 1194 (1932).
[233] L. Ruzicka and Thomann, *Helv. Chim. Acta*, **16**, 216 (1933).

genation of cholesterol and other sterols has apparently not been established. On the other hand, a different type of cyclization was discovered in connection with both cholic acid and the various sterols. According to Bachmann, Cook, Hewett, and Iball,[138] the product obtained from cholic acid by this type of dehydrogenation had the constitution of a 5-methyl-2′,1′-naphtho-1,2-fluorene (XXXIX). The formation of this product is possibly explained by the simple cyclization of the side chain with the carbon atom in position 16 in the sterol skeleton. The hydrocarbons obtained by the analogous dehydrogenation of cholesterol, ergosterol, and the phytosterols,[198,234] which should have a substituent in the 8 position on the basis of this reaction mechanism, do not possess the expected constitution,[138] although from their absorption spectra[197] they probably contain the naphthofluorene nucleus.

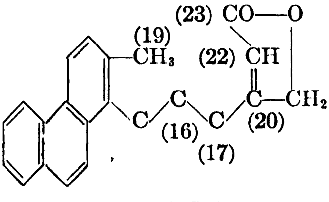


(XXXIX)

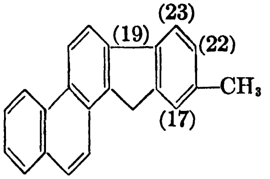
Bergmann has suggested[235] that these compounds may be 5,7-disubstituted naphthofluorenes, the formation of which would parallel the formation of 7-methylnaphthofluorene by the dehydrogenation of strophanthidin[236] (Formulas XL to XLII). It is interesting that all these cyclizations



(XL)



(XLI)



(XLII)

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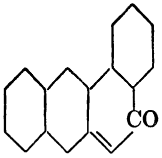
[234] Diels, Gädke, and Körding, *Ann.*, 459, 1 (1927).
[235] Bergmann, *J. Am. Chem. Soc.*, 60, 2306–2307 (1938).
[236] Elderfield and Jacobs, *J. Biol. Chem.*, 107, 143–154 (1934).

take place at lower temperatures than does the well known formation of chrysene.

The type of cyclization which results from the dehydrogenation of the monocyclic sesquiterpene alcohols with selenium or sulfur, and which leads to eudalene,[237] is still not entirely explained.

OTHER REARRANGEMENTS. In conclusion, brief mention should be made of several isolated and so far unexplained rearrangements which have been observed in various dehydrogenation reactions.

Examples of these are the formation of phenanthrene (with sulfur) from a hydrocarbon which is considered to be 1-cyclopentylindane,[238] and the formation of chrysene from the compound XLIII (with platinum black at 300° to 320°C.).[239] In both cases accurate data are lacking.



(XLIII)

Also, it is still unexplained why the homogeneous sesquiterpene alcohol guaiol yields a different azulene when selenium is used for the dehydrogenation than when sulfur is used.[133] This result may be due to a displacement of an alkyl group caused by the higher reaction temperature of selenium dehydrogenation.[240] Two different azulenes may also be obtained from ledol by similarly varying the reaction conditions.[241] The formation of naphthalene derivatives by the dehydrogenation of sesquiterpene compounds with an azulene structure[242] has not been thoroughly investigated. Similar rearrangements occur, however, even when azulenes are heated in the absence of dehydrogenation reagents.[240]

VIII. PARTIAL DEHYDROGENATION

In connection with partial dehydrogenations, two points which especially concern the preparative use of the method will be mentioned briefly.

Although partial dehydrogenations, in general, are likely to be rather undesirable for analytical purposes, they are frequently useful in preparative work. Sulfur, used in proportionately smaller amount, or perhaps the catalytic method, is probably preferable to selenium for this work.

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[237] L. Ruzicka and van Veen, *Ann.*, 476, 70–112 (1929).

[238] R. Robinson, *J. Chem. Soc.*, 1936, 80.

[239] J. W. Cook and Lawrence, *J. Chem. Soc.*, 1937, 817–827.

[240] Unpublished researches of the author.

[241] Nyman and Mikander, *Suomen Kemistilehti*, 14 B, 3–4 (1941); *Chem. Abstracts*, 35, 4755 (1941).

[242] Pfau and Plattner, *Helv. Chim. Acta*, 23, 768–792 (1940).

Von Braun and Irmisch[243] were able to obtain octahydrochrysene from dodecahydrochrysene by the use of 2 atoms of sulfur. Dimeric cyclohexadiene can be converted into a tetralin with a methylene bridge.[176] Several examples of partial dehydrogenation are to be found in the work of Cook and co-workers.[118,173,244] One of the best examples of this type of reaction is the partial dehydrogenation of neoergosterol, carried out by Honigmann[53] (Formulas VI and VII).

IX. DISPROPORTIONATION

The so called disproportionations are of particular importance, especially in catalytic dehydrogenation. In the presence of platinum metal catalysts, even at relatively low temperatures, unsaturated compounds, such as cyclohexadiene, are converted into mixtures of aromatic and completely saturated hydrocarbons.[245] This type of reaction seems to have been first observed by Knoevenagel and co-workers.[246]

Wieland[247] later showed that dihydronaphthalene is converted into naphthalene and tetralin in the presence of palladium black, with the evolution of heat. These reactions are completely understandable from the standpoint of the thermodynamic relationships, as Böeseken,[248] for example, has shown. A most thorough study of these disproportionations has been made by Zelinsky and by Linstead and co-workers. In the course of their investigations they surveyed cyclohexene,[245] various methylcyclohexenes,[249] terpenes, such as limonene[65,250] and α-pinene,[65,216] and also compounds with unsaturated side chains.[116,117] The work of Linstead especially[64,65,129,132] shows that disproportionations play an extremely important role in catalytic dehydrogenation.

In this connection it is interesting to note that the dehydrogenation tendency of tetralin can be utilized for the hydrogenation of a variety of unsaturated compounds,[251-253] corresponding to a disproportionation reaction between dissimilar molecules. Benzene has also been used as a hydrogen acceptor in catalytic dehydrogenation.[254]

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[243] von Braun and Irmisch, *Ber.*, **65 B**, 883 (1932).

[244] J. W. Cook and Haslewood, *J. Chem. Soc.*, **1934**, 428–433.

[245] Zelinsky and Pavlov, *Ber.*, **66 B**, 1420 (1933).

[246] Knoevenagel and Heckel, *Ber.*, **36**, 2816–2822 (1903); Knoevenagel and Fuchs, *ibid.*, 2848–2857; Knoevenagel and Bergdolt, *ibid.*, 2857–2861.

[247] Wieland, *Ber.*, **45**, 484 (1912).

[248] Böeseken, *Rec. trav. chim.*, **37**, 255 (1918).

[249] Zelinsky, *Ber.*, **57 B**, 2055 (1924).

[250] Zelinsky, *Ber.*, **57 B**, 2058–2059 (1924).

[251] Akabori and Suzuki, *Proc. Imp. Acad. Tokyo*, **5**, 255–256 (1929).

[252] See also Kindler and Peschke, *Ann.*, **501**, 191 (1933).

[253] Orchin, *J. Am. Chem. Soc.*, **66**, 535–538 (1944).

[254] Adkins, Richards, and Davis, *J. Am. Chem. Soc.*, **63**, 1320–1325 (1941).

Similar dismutations[121] can take place during chemical dehydrogenation and have been discussed in the section on hydrogenation effects. For this reason, it is understandable that completely saturated compounds are often obtained in addition to the aromatic dehydrogenation products. As a matter of fact, the removal of the calculated amount of hydrogen is seldom achieved in catalytic dehydrogenation. However, the yields of aromatic products obtained by disproportionation are usually sufficient to identify the *dehydrogenation products,* even with reactions in the sealed tube, where hydrogenation is certain to occur to a considerable extent.

An interesting example of disproportionation is the isomerization of 2,6-dibenzalcyclohexanone to 2,6-dibenzylphenol by palladium-charcoal at 235° to 245°C.[255]

X. HETEROCYCLIC COMPOUNDS

So far, the discussion has been confined almost exclusively to the dehydrogenation of isocyclic compounds. Recently, the various methods of dehydrogenation, particularly the catalytic methods, have also been applied successfully to heterocyclic compounds, of which those containing nitrogen have been fairly thoroughly investigated. The behavior of piperidine in reactions over platinum and palladium catalysts has been described in detail.[256] Pyrrolidine[257,258] and its derivatives[259–261] can be readily dehydrogenated to pyrroles. In like manner, nicotine is rapidly converted into nicotyrine.[262,263] Sulfur has also been used for this last dehydrogenation, although the yields are very unsatisfactory.[264] Decahydroquinoline[265,266] and decahydroisoquinoline[267,268] are dehydrogenated very readily. In this connection it is interesting to note that 5,6,7,8-tetrahydroquinoline can be obtained[265] by the partial dehydrogenation of decahydroquinoline, indicating that the ring containing the nitrogen atom exhibits the greater dehydrogenation tendency. This procedure is very valuable from the preparative standpoint, since only 1,2,3,4-tetrahydroquinoline can be obtained by the hydrogenation of quinoline. 2-Alkylimidazolines are dehydrogenated to the corresponding imidazoles by various metallic catalysts including platinum and palladium.[269]

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[255] Horning, *J. Org. Chem.*, **10,** 263–266 (1945).

[256] Zelinsky and Borisov, *Ber.*, **57 B,** 150 (1924).

[257] Zelinsky and Yur'ev, *Ber.*, **64 B,** 101 (1931).

[258] Wibaut, Molster, Kauffmann, and Lenssen, *Rec. trav. chim.*, **49,** 1127–1130 (1930).

[259] Zelinsky and Yur'ev, *Ber.*, **62 B,** 2589–2590 (1929).

[260] Ehrenstein, *Ber.*, **64 B,** 1137 (1931).

[261] Yur'ev and Shen'yan, *J. Gen. Chem.* (*U. S. S. R.*), **4,** 1258–1261 (1934).

[262] Wibaut and Overhoff, *Rec. trav. chim.*, **47,** 935–939 (1928).

[263] Frank, Holley, and Wikholm, *J. Am. Chem. Soc.*, **64,** 2835–2838 (1942).

[264] Morton and Horvitz, *J. Am. Chem. Soc.*, **57,** 1860–1861 (1935).

[265] Ehrenstein and Bunge, *Ber.*, **67 B,** 1715–1729 (1934).

[266] Yur'ev and Mironenko, *Sci. Repts. Moscow State Univ.*, **1936,** No. 6, 277–279; *Chem. Zentr.*, **1937, II,** 2356.

[267] Späth and Polgar, *Monatsh.*, **51,** 190–204 (1929).

[268] Späth, Berger, and Kuntara, *Ber.*, **63 B,** 134 (1930).

In other cases the breaking up of rings, ring closures, and rearrangements result.[225,270] Prelog and co-workers[271,272] have reported a rearrangement which occurs in the dehydrogenation of 3-acetylpiperidine derivatives with selenium at 300°C. The corresponding 2,3-dimethylpyridine is obtained instead of the expected 3-ethylpyridine. The same author has also investigated the dehydrogenation of some azabicycloparaffins with selenium or palladium-charcoal at 350°C.[273] 1-Azabicyclo[2.2.1]heptane gave γ-picoline, 1-azabicyclo[2.2.2]octane gave 4-ethylpyridine, and 1-azabicyclo[2.2.0]decane yielded a small amount of quinoline.

Späth and co-workers have applied catalytic dehydrogenation with great success to their researches on alkaloids.[274]

A number of experiments on heterocyclic substances containing oxygen and sulfur have also been published. Dihydrocoumarins can be dehydrogenated to coumarins,[275] hydrofuranes to furanes, and tetrahydrothiophene to thiophene.[276,277]

XI. SECONDARY REACTIONS

In the foregoing discussion, in general only those examples of dehydrogenation reactions which yielded aromatic dehydrogenation products have been considered. Various interferences can also take place, especially by the action of sulfur on organic compounds, and in many cases result in a greatly lowered yield of the normal dehydrogenation products. A compilation of the older literature on this subject is found in the frequently cited treatise by Ruzicka.[278] A product containing sulfur has been isolated from the dehydrogenation of elemol,[237] to mention one of the more recent observations. Fieser has reported a similar experience.[279] Since the presence of these by-products does not greatly increase the difficulty of working up the aromatic hydrocarbon, however, the scope of the dehydrogenation is not greatly changed.

Selenium is less readily introduced into organic molecules,[23] which probably accounts for the general applicability of this reagent.

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[269] Gränacher and J. Meyer, German Patent, 703,899, Feb. 13, 1941; *Chem. Abstracts*, **36**, 1045 (1942).

[270] Ehrenstein and Marggraff, *Ber.*, **67 B**, 486–491 (1934).

[271] Prelog, Komzak, and Moor, *Helv. Chim. Acta*, **25**, 1654–1664 (1942).

[272] Prelog, Moor, and Führer, *Helv. Chim. Acta*, **26**, 846–848 (1943).

[273] Prelog and Balenovic, *Ber.*, **74 B**, 1508–1510 (1941).

[274] See the summary by Späth and Galinovsky, *Ber.*, **69 B**, 2059–2061 (1936).

[275] Späth and Galinovsky, *Ber.*, **70 B**, 235–238 (1937).

[276] Yur'ev and Borisov, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 138 (1937).

[277] Yur'ev and Borisov, *Ber.*, **69 B**, 1395–1398 (1936).

[278] See p. 12 of Ruzicka's report (footnote 1).

[279] L. F. Fieser, *J. Am. Chem. Soc.*, **55**, 4977–4984 (1933).

XII. DEHYDROGENATION TECHNIQUES

1. Sulfur

The original procedure described by Ruzicka and co-workers[1,3] is still employed, as a rule, for dehydrogenations with sulfur. The exact, calculated amount of sulfur is always used; an excess should be avoided because of the danger of secondary reactions. The evolution of hydrogen sulfide usually begins at about 180°C. and is complete in a few hours. Rapid temperature increase at the start of the reaction should be avoided, since there is danger of frothing over, especially with large runs. Toward the end of the reaction, the temperature may, if necessary, be raised to approximately 260°C., although prolonged heating at higher temperatures in the presence of unchanged sulfur should be avoided. A temperature of 200° to 220°C. can be regarded as normal. In many cases it has proved useful to carry out the dehydrogenation under a slight vacuum.[280]

The first step in the working up of the reaction mixture is almost always a direct vacuum distillation of all the volatile material. The distillate usually contains some sulfur. It is not advisable, however, to attempt to remove sulfur by distillation over sodium, since part of the aromatic hydrocarbon is also destroyed by this procedure. Usually after a second distillation, the separate fractions are sufficiently pure for preparing the picrate or trinitrobenzene derivative, or for other means of identification.

2. Selenium

The material to be dehydrogenated is heated with the calculated amount of amorphous or crystalline powdered selenium[146] in a flask with a sealed-on reflux condenser. The use of an excess of selenium is not generally detrimental. The evolution of hydrogen selenide begins at about 250° to 280°C., and can readily be followed by the progressive coloration in a tower of bleaching powder. The temperature, which should always be closely controlled by use of a metal bath, is slowly raised as necessary. Temperatures up to 350°C. can be considered safe. Experience has shown that much above this limit, various rearrangements may be expected. In general, dehydrogenations with selenium appear to proceed much more slowly than those with sulfur, and often very long reaction times are employed (20 to 100 hours). It must be remembered, however, that too long heating at high temperature may cause unnecessary decomposition of the reaction products. For example, according to Nagel and Körnchen,[281] 12 hours of heating at 280° to 305°C. are the best conditions for the preparation of retene from rosin oil. In many other cases, still shorter reaction times suffice.

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[280] Melville, *J. Am. Chem. Soc.*, 55, 2462–2465 (1933).

[281] Nagel and Körnchen, *Chem. Umschau Fette, Öle, Wachse, Harze*, 39, 1 (1932).

For working with fairly volatile materials or with very small amounts, dehydrogenation with selenium in the sealed tube has proved very satisfactory.[56,112,134] After the reaction is complete, the mixture is usually extracted with ether or benzene, and the residue from the evaporation of the extracts is then fractionated and further worked up.

3. Catalytic Methods

Experience has shown that the method of preparation of dehydrogenation catalysts greatly influences their activity and in many cases also their effect on the organic compounds. Zelinsky and co-workers,[18,256,282,283] in particular, have made a systematic study of this subject. On the basis of their results, the use of palladium-charcoal has come into considerable favor. Precise directions for the preparation of dehydrogenation catalysts have been given by Zelinsky and Turova-Pollak,[18] Diels and Gädke,[194] and Packendorff and Leder-Packendorff,[284] among others. Recently, Linstead and co-workers compared the activities of catalysts prepared in different ways, under conditions which are readily adaptable to practical requirements.[129,132] They arrived at the following conclusions.

1. Very active catalysts result from the method of Willstätter and Waldschmidt-Leitz,[285] but somewhat higher activity and better reproducibility are obtained if the metal is precipitated in slightly higher dilution.

2. Platinum and palladium catalysts prepared under the same conditions have very similar activity. Palladium seems to be somewhat more inclined to cause side reactions.

3. The activity of both these metals is very dependent on the nature of the carrier and decreases in the following order: metal on activated charcoal > metal on asbestos > metal as "black."

4. The course of the dehydrogenation of substances with quaternary, cyclic carbon atoms is strongly influenced by the catalyst carrier, but not by the choice of the metal.

Apparatus for catalytic dehydrogenation in the vapor phase has been described at various times.[24,286,287] In the determination of constitution, however, the use of relatively simple apparatus is preferable, and dehydrogenation in the liquid phase has been tried by simply heating the com-

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[282] Zelinsky, *Ber.*, **59 B**, 156–162 (1926).
[283] Zelinsky and Pavlov, *Ber.*, **56 B**, 1250 (1923).
[284] Packendorff and Leder-Packendorff, *Ber.*, **67 B**, 1388–1391 (1934).
[285] Willstätter and Waldschmidt-Leitz, *Ber.*, **54**, 123 (1921).
[286] See, for example, L. Ruzicka and Stoll, *Helv. Chim. Acta*, **7**, 84 (1924).
[287] Levitz and Bogert, *J. Am. Chem. Soc.*, **64**, 1719–1720 (1942).

pound in the presence of the catalyst.[194,288] Since in general the main requirement is only that the temperature necessary for dehydrogenation be attained, this simple procedure can give good results for all substances that boil at 300°C. or higher under atmospheric pressure. It is of practical importance that a number of the more volatile compounds, such as terpenes and sesquiterpenes, can also be treated in this manner, because at their boiling point they are dehydrogenated or disproportionated to aromatic compounds.[65] These disproportionations can be carried out with good results in the sealed tube, a procedure which is especially recommended for very small amounts of material.

The temperature and duration of catalytic dehydrogenation naturally vary within wide limits. As a matter of information, tetralin has been smoothly dehydrogenated at temperatures as low as 180°C., but decalin and 9-methyldecalin only at 300° to 350°C.[129,132] At temperatures much in excess of 350°C., many secondary reactions may be expected.

For dehydrogenatious in the liquid phase, palladium-charcoal in the amount of 10 to 50% of the weight of the material is commonly used; the catalyst in turn usually contains 10 to 30% of the metal. Because of the relatively high price of the platinum metals, it is important that they can be regenerated from the spent catalyst and used again without detriment. According to Linstead,[132] the method of Baldeschwiler and Mikeska[289] gives good results for the recovery of platinum, and that of Keiser and Breed[290] for palladium.

4. Solvents

Occasionally, dehydrogenations with sulfur and selenium, especially those used for preparations, have been carried out in the presence of solvents such as naphthalene,[65] quinoline,[291,292] and acetanilide.[293] A series of other solvents was investigated by Morton and Horvitz[364] in connection with the dehydrogenation of nicotine with sulfur. The use of solvents is likely to be more advantageous in catalytic dehydrogenations, however. The yields of phenols from alcohols and ketones, especially, can be significantly increased by the use of mesitylene or *p*-cymene as a diluent.[64] A thorough investigation has been made of the influence of various solvents on the dehydrogenation of 1- and 4-keto-1,2,3,4-tetrahydrophenanthrene to

[288] See L. Ruzicka and Waldmann, *Helv. Chim. Acta*, **18**, 611–612 (1935); Waldmann, Dissertation, Eidgenössische Technische Hochschule, Zurich, 1935.

[289] Baldeschwiler and Mikeska, *J. Am. Chem. Soc.*, **57**, 977–978 (1935).

[290] Keiser and Breed, *Am. Chem. J.*, **16**, 20 (1894).

[291] Winterstein, Vetter, and Schön, *Ber.*, **68 B**, 1079–1085 (1935).

[292] L. F. Fieser, M. Fieser, and Hershberg, *J. Am. Chem. Soc.*, **58**, 1463–1468 (1936).

[293] Diels and Stephan, *Ann.*, **527**, 279–290 (1937).

1- and 4-phenanthrol, respectively,[64,294] and of a number of isomeric ketohexahydrochrysenes to the corresponding chrysenols.[62,63]

5. Development and Identification of Dehydrogenation Products

Since complex mixtures of various reaction products may usually be expected from dehydrogenation, as is always the case for example with the triterpenes, a very careful fractional distillation is recommended as the first step. The individual fractions are then freed of phenols if necessary, and finally purified further by recrystallization of the picrate or trinitrobenzene derivative. Even an approximately quantitative separation of these mixtures is a lengthy and difficult procedure. The preparation of picrates, which can readily be decomposed by sodium hydroxide or ammonia, was originally the principal means of isolating the individual dehydrogenation products, but more recently the trinitrobenzene derivatives have also been frequently employed. In general, these appear to be rather less soluble and somewhat more stable than the picrates, and can equally well be resolved chromatographically on aluminum oxide. This last method for the resolution and regeneration of the free hydrocarbons is also recommended for the picrates, because of its neatness and simplicity.[12] If the picrates cannot be obtained directly from the fractionated dehydrogenation products by treatment with alcoholic picric acid solution, Ruzicka[1] recommends that the alcohol be allowed to evaporate in a porcelain dish. In the residual oil, the traces of picrates, which almost without exception crystallize in small needles, are then readily distinguishable from the nearly colorless plates of crystalline picric acid. The needles can be freed from adhering oil on a clay plate.

The positive identification of even known dehydrogenation products is sometimes difficult. For example, the work of Ruzicka and co-workers[50,295] has shown that the picrates and trinitrobenzene derivatives of the different trimethylnaphthalenes give only very slight, if any, depression in the mixed melting point. Whenever their preparation is possible, therefore, the styphnates and trinitrotoluene derivatives, or oxidation products of the hydrocarbons, such as quinones, may be used as an additional help in identification.

Absorption spectra have been of the greatest importance in furnishing information on the nature of the ring system of high molecular weight dehydrogenation products.

XIII. CONCLUSION

The value of dehydrogenation methods for determining constitution has frequently been questioned. The results have often been regarded as

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[294] Mosettig and Duvall, *J. Am. Chem. Soc.*, 59, 367–369 (1937).
[295] L. Ruzicka and Ehmann, *Helv. Chim. Acta*, 15, 140–162 (1932).

unreliable, particularly because of the numerous changes which may occur in the carbon skeleton. However, these rearrangements, in the main, conform to definite reactions which may be regularly formulated. Frequently, moreover, the results of the dehydrogenation itself have proved on more careful study to be valid, and the rearrangements to be merely a result of the synthetic methods used. In addition, these secondary reactions can often be avoided by careful manipulation, such as more accurate control of temperature. In view of this, an important task for the future will be detailed reinvestigation of the early results obtained on natural products, possibly by means of type experiments. The dehydrogenation conditions, especially the temperature, are doubtless most important in weighing the reliability of the results, and accurate knowledge of their influence can help to avoid false conclusions.

Dehydrogenation is very useful as a quick source of information on the general nature of alicyclic compounds. The relationship of the cardiac aglucons to the sterols, for example, was established for the first time by means of dehydrogenation. Also, the question of whether the various sapogenins belong to the sterol or to the triterpene series can be readily decided on the basis of dehydrogenation results.[296,297]

The role which dehydrogenation, along with the isoprene hypothesis and the analytical methods, has played in the study of the polyterpenes, particularly the pentacyclic triterpenes, was recognized several years ago by Ruzicka.[8] Although there are still a number of questions, which perhaps can be answered only by systematic analysis, dehydrogenation nevertheless first made possible a fuller understanding of this difficult field. The great importance of dehydrogenation in other fields, also, is generally recognized today, and indeed there are few methods which can compete with it in the determination of the carbon nuclei of complex natural products.

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[296] L. Ruzicka and van Veen, *Z. physiol. Chem.*, **184,** 69–82 (1929).

[297] Schulze, *Z. physiol. Chem.*, **238,** 35–53 (1936).

Reductions with Raney Nickel Catalysts

BY R. SCHRÖTER

Translated and revised by I. SALMINEN

I. INTRODUCTION

In 1925 and 1927 Raney disclosed a novel method for the preparation of catalysts.[1] The method described in his patents consists of alloying a catalytically active metal with one which is catalytically inactive. The inactive component is then dissolved either completely or partially from the alloy, leaving behind a metal which was claimed to be very active.

Similar methods were patented by other authors at about the same time in Germany and in England.[2] A third group of authors obtained a patent in this field at a later date.[3]

Raney claimed protection both for the use of the alloys as catalysts and for the preparation of catalysts.[1] Nickel was usually the active component in the alloys, whereas silicon, aluminum, magnesium, and zinc were the inactive components. After grinding, the alloy is treated in any of several ways:

1. The catalytically inactive portion is removed by a solvent which does not attack the active substance.

2. The alloy is decomposed with caustic alkali.

3. The alloy is decomposed with alkali carbonates.

4. The alloy is treated with water at high temperatures and pressures.

5. The alloy as such, or after treatment with alkaline solution, is used with hydrogen at high temperature and pressure.

Only the second of these methods of decomposition gave metals which became known in the literature as Raney catalysts, and aluminum proved to be the most useful metal employed as the inactive component of the alloys.

Aluminum of the required degree of purity is readily obtained. Pure silicon is about as useful as aluminum. For the synthesis of hydrocarbons from carbon oxides and hydrogen, Fischer and Meyer[4] made use of silicon, as well as aluminum, in the preparation of alloys with nickel, cobalt, cobalt-nickel, and iron. They found that cobalt-silicon or cobalt-nickel-silicon alloys gave exceptionally good catalysts for their purposes. Fischer and Meyer termed these catalysts very active, probably referring to the reducing, condensing, or polymerizing activity necessary for hydrocarbon syntheses. In those cases in which pure hydrogen was added, nickel catalysts derived from nickel-aluminum alloys were more active than those from nickel-silicon alloys.[5] Rapoport and Siltschenko[6] compared silicon alloys with those from aluminum but found little difference in their action for pressure reductions. The results obtained with technical silicon were unsatisfactory because of the iron content. It is known that iron decreases the activity of Raney catalysts as soon as it exceeds the usual content of 0.3 to 1%.

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[1] Raney, U. S. Patents, 1,563,787 (Dec., 1925); 1,628,191 (May, 1927); 1,915,473 (June, 1933); Canadian Patent, 315,299 (Oct., 1934); French Patent, 729,357 (Dec., 1932).

[2] German Patent, 408,811 (Apr., 1923); British Patent, 282,112 (Dec., 1927).

[3] Russian Patent, 38,127 (1933).

No publications were found on the use of zinc and magnesium as the inactive components.

II. PREPARATION OF RANEY CATALYSTS

The following steps are required for the preparation of Raney catalysts: fusion, pulverization, decomposition of the alloy, and washing of the active metal. A few general directions will be given for the preparation of the catalysts. Although these directions have been accumulated mostly for Raney nickel, and apply in a strict sense only to this catalyst, they may also serve as guides for the preparation of other active metals.

1. Fusion of Alloy

The alloys can be prepared by comparatively simple means, because the fusion of aluminum with most heavy metals is strongly exothermic. It suffices to melt the aluminum and then to heat the melt at 900° to 1200°C. The melt is protected against oxidation by an inert gas or by one of the salt fluxes used in working with aluminum. On introduction of the second metal component enough heat is generated to reach the fusion temperature of the alloy. For example, when nickel is added to aluminum which has been preheated to 900° to 1200°C., the temperature rises to about 1500°C. This temperature is higher than that necessary to give the nickel-aluminum alloy. An alloy of the composition $Ni\text{-}Al_2$, containing 52.1% Ni, melts at 1400°C. and an alloy of the composition $Ni\text{-}Al_3$, containing 42% Ni, melts at 1130°C. The alloys can also be produced from the heavy metal oxides and aluminum powder in a thermite process. It is claimed that the method of preparing the alloy has no bearing on the quality of the catalyst.[7]

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[4] Fischer and Meyer, *Ber.*, **67**, 253 (1934).

[5] Schwab and Zorn, *Z. physik. Chem.*, **32 B**, 169 (1936).

[6] Rapoport and Siltschenko, *Chem. J., Series B, J. Appl. Chem.* (*U. S. S. R.*), **10**, 1427 (1937).

However, the composition of the alloy greatly affects the latter. Raney claimed that he was able to prepare useful catalysts from alloys containing 10 to 85% Ni, or 15 to 90% Al. This claim is only partially borne out by other investigators. Dupont and Piganiol[8] prepared Ni-Al alloys based on the phase diagrams of Gwyer.[9] These alloys contained 18 to 67% Ni. When the active nickel obtained from these alloys was studied, little difference was found in catalysts derived from alloys containing from 30 to 50% Ni. The activity of catalysts derived from alloys with more than 50% Ni decreased rapidly with increasing amounts of nickel. An alloy containing 67% Ni, corresponding to the composition Ni-Al, no longer gave an active catalyst, because the alloy was not decomposed by sodium hydroxide. Similar results were obtained with nickel-silicon alloys. An alloy of the composition $Ni\text{-}Si_2$ was attacked by hot alkali only with difficulty. Copper-aluminum alloys of a low aluminum content are scarcely attacked by alkali.

There appears to be no lower limit for the amounts of active metals in alloys. Nickel-aluminum alloys containing less than 30% Ni probably show increased activity. However, the increase does not seem to be great enough to warrant the use of such dilute alloys. For all practical purposes, an alloy range of 30 to 50% of active metal is most suitable.

2. Pulverization

Aluminum alloys are attacked by alkali even as lumps, but rather slowly, and the gross structure is partially retained. Inasmuch as the active metals are needed in a finely divided state, pulverization is therefore necessary before the alkali treatment. The ease with which alloys can be pulverized varies. An alloy containing 50% Al and 50% Ni is very brittle and can be broken up readily. The alloys become tougher with increasing aluminum content and large pieces can be broken up only with difficulty. Turning on a lathe has proved to be a good method for working rather large castings of alloy, because these alloys crumble without producing long ribbons of metal. The rather finely crystalline material obtained in this way can be powdered in a ball mill. Rapoport and Siltschenko[6] believe they have shown that the particle size of the substance to be decomposed has some influence on the activity of the catalyst. They claim that catalysts prepared from substances varying in particle size from dust to 2.5 mm. in diameter show the same activity, but that the activity decreases rapidly as the particle size increases. However, catalysts prepared from alloys of large particle size are still so active that they are more suitable than closely packed ones for continuous reductions in the gas or liquid phase.[10]

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[7] Ruggli, *Helv. Chim. Acta*, **22**, 478 (1939). Faucounau, *Bull. soc. chim.*, **4**, 63 (1937).

[8] Dupont and Piganiol, *Bull. soc. chim.*, **6**, 322 (1939).

[9] Gwyer, *Z. anorg. allgem. Chem.*, **57**, 113 (1908).

3. Decomposition of Alloy and Washing of Active Metal

As has been pointed out already, it is necessary to treat the alloys with alkalies to dissolve the aluminum (or silicon) from Raney catalysts. In other methods of decomposition the aluminum remains in the catalyst as the oxide or hydroxide and becomes a carrier for the finely divided active metal. Approximately 30% sodium hydroxide is used for the decomposition. The alloy may be added to the alkali, or the alkali may be added to a suspension of the alloy in water. The decomposition takes place with a strong evolution of hydrogen. Since the decomposition is exothermic, it is advisable to moderate the reaction by initial cooling. Later on, the dissolving action is driven to completion by heating. Reports differ on the best temperature for the procedure. According to one author, the mixture is heated to a gentle boil; that is, to about 130°C. Paul and Hilly[11] claim that under these conditions the catalyst is contaminated by the separation of aluminum hydroxide and that the activity is decreased. According to them, a temperature of 100°C. is suitable for removal of the aluminum. They also claim that the lower temperature is preferred, because many active metals decompose water at higher temperatures and in this way become oxidized.

After the decomposition, some unattacked aluminum remains in the active metal. It is claimed that the residual aluminum, which may amount to several per cent, is beneficial. If this aluminum is removed by exhaustive treatment with alkali, the metal becomes inactive.[12]

For lack of systematic study it is not clear how much of the inactive component must be removed to give a catalyst of maximum activity. It has been customary to remove this component as completely as possible. According to the experiments of Rapoport and Siltschenko this complete removal is unnecessary. They claim that a usable catalyst is obtained after the removal of 10 to 25% of the aluminum. On removal of 40%, the catalyst is active and on further removal of aluminum reaches an optimum. The authors fail to mention where this optimum point occurs.. Bag and co-workers[13] have found that the optimum activity of a catalyst to be used in the reduction of fats is obtained when 8% of the aluminum is removed from the nickel-aluminum alloy. The Hercules Powder Company,[14] in the manufacture of catalysts for continuous reductions, uses alloys prepared according to the Raney method. Only part of the inactive component is removed from these catalysts. Such catalysts have the advantage that they can be reactivated by further treatment with alkali.

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[10] Hercules Powder Co., French Patent, 825,520.

[11] Paul and Hilly, *Bull. soc. chim.*, **3**, 2330 (1936).

[12] Aubry, *Bull. soc. chim.*, **5**, 1333 (1938).

[13] Bag, Jegupow, and Wolokitin, *Chem. Abstracts*, **30**, 3439 (1936).

The active metal which separates as a heavy powder on treatment with alkali is separated from the solution of aluminate and excess alkali and washed carefully until the wash waters are neutral. The final traces of alkali are very difficult to remove. According to Aubry,[12] these traces protect the active metal by preventing it from being oxidized by the water. If all traces of alkali are removed, Raney nickel is converted slowly by water to nickel hydroxide with the evolution of hydrogen. Raney catalysts are unstable in air and more or less pyrophoric. For this reason they must be stored under water, alcohol, or other inert solvent.

4. Specific Procedures

A. Nickel

Directions have been published for the preparation of active nickel by investigators who include Covert and Adkins, Paul and Hilly, Dupont and Piganiol, Ruggli,[7] Calas,[15] and Mozingo.[16]

These directions differ as to the nickel content of the alloys and in the technique of their decomposition. The directions of Paul and Hilly[11] are given here.

400 g. of aluminum are melted and heated to 1200°C. To this melt are added, all at once, 300 g. of nickel in the form of small cubes. This cubic nickel is better suited for making the alloy than compact, machine-worked metal, because the somewhat porous structure allows the nickel to be dissolved readily in the aluminum during the rather low initial temperature. The nickel dissolves with a vigorous reaction and the temperature rises approximately to 1500°C. After cooling, the alloy is broken by hammering and pulverized. Two hundred and fifty grams of the alloy are added in small portions to 1 liter of 25% sodium hydroxide with external cooling in an ice bath. The decomposition takes place, accompanied by foaming, spattering, development of heat, and evolution of hydrogen. When all of the metal has been added, the temperature is raised and held at 90° to 100°C. until the evolution of hydrogen slackens. The mixture is allowed to settle; it is decanted and the alkali treatment is repeated with 1 liter of fresh alkali. After removal of this last alkali

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[14] Hercules Powder Co., U. S. Patent, 2,094,117.
[15] Calas, *Bull. soc. chim.*, **6**, 1393 (1939).
[16] Mozingo, *Organic Syntheses*, **21**, 15 (1941).

by decantation, the nickel is washed repeatedly by trituration and decantation with water, until the wash water is neutral to phenolphthalein. The water is then displaced by alcohol and the catalyst stored under alcohol in well filled bottles.

An excellent method for the preparation of Raney nickel catalyst is given by Mozingo.[16] His directions indicate a nickel-aluminum alloy to be used as the starting material. This alloy is readily available in this country.

Raney nickel can be activated by other metals. Such claims have been made for Cu, Co, Cr, and Zn, but details on the use of these metals are not given. Activation of the finished catalyst by the introduction of small amounts of noble metals, especially platinum is recommended. This activated Raney nickel, proposed by Delépine and Horeau[17] and studied by Lieber and Smith,[18] has a very high degree of activity.

Recently Jayme and Satre[19] have also described a catalyst activated in a similar fashion. This catalyst was used with good results in the reduction of sugars.

B. Cobalt

The preparation of active cobalt has been described by Faucounau,[20] Dupont and Piganiol,[8] Fischer,[4] and in the U. S. Patent, 2,166,183, granted to du Pont. The French authors prepared the catalyst from nickel-free cobalt oxide by the alumino-thermal method. The alloy is slag-like and gives a moderately active metal. It is necessary to dissolve the initial alloy in additional aluminum to obtain a metal which will be a suitable catalyst after the decomposition. This method is probably feasible if one is willing to work with pure cobalt as the catalyst and has nickel-free metal at his disposal. Otherwise, the method of the du Pont patent, in which technical cobalt is used, is recommended. The Al-Co alloy is prepared in the same way as is Al-Ni. The decomposition is effected as follows:

50 g. of finely powdered Al-Co alloy, consisting of equal parts by weight of cobalt and aluminum, are suspended in 300 cc. of boiling water. A solution of 50 g. of sodium hydroxide in 100 cc. of water is added slowly to the suspension with good stirring, and the mixture is boiled for 4 hours. The supernatant solution is decanted and the residue boiled again for 4 hours with a solution of 50 g. of sodium hydroxide in 300 cc. of water. The catalyst is washed free from alkali by repeated decantations with water and stored under alcohol.

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[17] Delépine and Horeau, *Bull. soc. chim.*, 4, 31 (1937).

[18] Lieber and Smith, *J. Am. Chem. Soc.*, 58, 1417 (1936).

[19] Jayme and Satre, *Ber.*, 77, 251 (1944).

[20] Faucounau, *Bull. soc. chim.*, 4, 63 (1937).

The same patent describes another Raney cobalt in which the aluminum is only partly removed. This catalyst is claimed to be especially suitable for the preparation of primary amines from nitriles. The catalyst may be obtained as a powder which is no longer pyrophoric by exercise of suitable precautions, such as careful drying in a vacuum with exclusion of air and subsequent careful oxidation with air at a temperature of less than 30°C.

C. Copper

Faucounau[21] described the preparation of an active copper made in essentially the same way as the Raney nickel described by Paul and Hilly. He started with an alloy, the so called Dewarda alloy, consisting of 50% Al, 45% Cu, and 5% Zn, which has been used occasionally in laboratories for reductions with nascent hydrogen. The finely powdered alloy was added to cooled 30% sodium hydroxide. After 12 hours the mixture was heated; on cessation of the hydrogen evolution the mixture was decanted. The treatment with fresh sodium hydroxide was repeated; the mixture was boiled for a short time, decanted, and washed neutral with water. The catalyst which was boiled for a short time, decanted, and washed neutral with water. The catalyst which was stored under alcohol contained 1.4% aluminum and 1.3% zinc, in addition to traces of iron and silicon.

D. Iron

At about the same time that Dupont and Piganiol reported their inability to prepare active manganese and iron by the Raney method, Paul and Hilly[22] described the preparation of an active iron from iron-aluminum alloy. Dupont and Piganiol obtained only oxides because of the instability of active iron in the presence of water. The directions of Paul and Hilly are as follows:

150 g. of finely powdered iron-aluminum alloy containing 20% iron are added in small portions to 1 liter of 25% sodium hydroxide in a hood. The reaction is extremely vigorous. When all of the alloy has been added, the mixture is heated for about 1 hour at 80° to 90°C. until the evolution of hydrogen ceases. The aluminate solution is decanted and replaced by 1 liter of fresh sodium hydroxide. The decomposition is repeated and the mixture heated for 1 hour. The alkali is poured off and the iron washed repeatedly by trituration and decantation with boiled water. The solid is then placed on a suction filter and washed with boiled water until the washings are neutral to phenolphthalein. The water is displaced by alcohol and the catalyst stored under absolute alcohol.

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[21] Faucounau, *Bull. soc. chim.*, **4**, 58 (1937).
[22] Paul and Hilly, *Bull. soc. chim.*, **6**, 218 (1939).

Raney iron reacts slowly with water even below 100°C. with the evolution of hydrogen. For this reason prolonged heating must be avoided during preparation of the catalyst. The catalyst contains 92% iron and 6% aluminum.

Dupont has attempted to obtain a few other metals in the Raney form. These metals include nickel-copper and nickel-cobalt. Nickel-copper is not of much interest for reducing purposes, because the copper decreases the activity of nickel considerably. The combination is said to be very active as a dehydrogenating catalyst. Nickel-cobalt, which Fischer prepared from Ni-Co-Si is more active than nickel or cobalt alone in the synthesis of straight chain hydrocarbons. According to Rapoport and Siltschenko this catalyst, obtained from Ni-Co-Al, is more active than the individual metals for the reduction of phenol and naphthalene. The method for preparing the active metal pairs is analogous to that for preparing active nickel or cobalt.

III. PROPERTIES OF RANEY METALS

The active metals are obtained as black to gray-black heavy powders which ignite in contact with air. They are by no means pure metals, but contain impurities such as traces of iron, copper, cobalt, manganese, and silicon which were present in the starting materials, as well as varying amounts of aluminum (up to 5%) and small amounts of alkali (0.1 to 0.6%). The finely divided metals are crystalline, just as are those derived by thermal methods. The essential difference lies in the size of the crystal. The active metal particles are 40 to 80 Å in diameter, or about one-tenth the size of metals obtained by the Sabatier method of preparation. It has been shown with nickel that the size of the crystals is independent of the concentration of the active metal in the alloy. The crystal forms of nickel and cobalt have been determined. Raney nickel crystallizes in the cubic system, just like nickel in other nickel catalysts. On the other hand Raney cobalt occurs in the hexagonal form, whereas catalysts prepared from this metal by thermal methods occur in the regular form. The conclusion of Dupont and Piganiol, that Raney cobalt does not show the expected activity because it occurs in the hexagonal form, is incorrect, because both forms of cobalt are catalytically active. But with nickel, only the cubic form is active; the hexagonal form is not.[23]

Raney catalysts contain hydrogen bound to the metal in some form. Part of this hydrogen can be removed by heating. The hydrogen is also lost slowly on storage of the catalyst. This loss is especially rapid in the presence of air. The activity of the catalyst declines as the hydrogen is released, but the two behaviors are not parallel. The active metals can be stored in well sealed containers without much loss of activity. Raney nickel, even after a year of storage, is still an excellent catalyst.

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[23] Le Clerc and Lefevre, *Compt. rend.*, **208**, 1650 (1939).

During the following discussion of the properties of Raney nickel the reader must not conclude that the properties which are discussed pertain only to this metal. It so happens that Raney nickel has been studied extensively as the first in the series of active metals. For this reason we must not exclude the possibility that other metals might show similar behavior on closer investigation.

1. Reducing Properties

The ability to promote reduction is the outstanding property of nickel, this property being attributable to its ability to join in some fashion with hydrogen. Freshly prepared Raney nickel contains so much hydrogen that its formula is nearly that of a "compound" Ni_2H. Raney nickel behaves electrochemically like a reversible hydrogen electrode and has the same reducing potential as platinized platinum and platinum black.

Without closer inspection we may attribute the reducing ability of Raney nickel to the hydrogen content. Raney nickel has the power to reduce permanganate to manganese dioxide, nitrites and nitrates to ammonia. Chlorates, bromates, iodates, hypochlorites, molybdates, tungstates, and ferric salts are also attacked by it. Dichromates and perchlorates are not affected. Among organic compounds, for example, nitrobenzene is reduced by Raney nickel with the formation of azo- and azoxybenzene; double bonds are reduced in the absence of molecular hydrogen. Because of this property the volume of absorbed hydrogen which is observed during the customary reductions of double bonds, with molecular hydrogen and Raney nickel as catalyst, is always too low. Depending on the size of batch being reduced and the amount of catalyst being used, the volume of hydrogen may vary as much as 10% from theory.

Mozingo and co-workers[24] tested this ability of Raney nickel to reduce compounds in the absence of molecular hydrogen. By heating an alcoholic solution of 5 to 10 g. of compound for 2 to 5 hours with 25 g. of Raney nickel, 50 to 95% of the compound was reduced.

Raney nickel, unlike usual nickel, is able to form an amalgam with mercury. This reaction is also attributable to the bound hydrogen which acts as the third component in the amalgam. Nickel which has been loaded cathodically with hydrogen behaves similarly. Bougault[25] recently showed that nickel dissolves quite generally in mercury if nascent hydrogen is present. On removal of the mercury by distillation from the nickel amalgam, a finely divided nickel residue is obtained, which is pyrophoric only if the amalgam was prepared originally from Raney nickel.

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[24] Mozingo, Spencer, and Folkers, *J. Am. Chem. Soc.*, **66**, 1859 (1944).

[25] Bougault, *Bull. soc. chim.*, **6**, 855 (1939).

2. Raney Nickel as Oxidation and Oxidation-Reduction Catalyst

Earlier we mentioned that Raney nickel has the ability to decompose water under some conditions. Hydrogen is evolved and the metal is oxidized to nickel hydroxide. However, if a readily oxidizable substance which can act as the oxygen acceptor is present in the aqueous solution, Raney nickel is unchanged and acts merely as a catalyst for the oxidation. Hypophosphites in the presence of Raney nickel are reduced to phosphites with strong evolution of hydrogen. Stannites are oxidized to stannates under the same conditions. With hypophosphites the reaction is quantitative. The course of the reaction can be followed by acidimetric titration with hypophosphorous acid. In addition to acting as an oxidation catalyst, Raney nickel retains its function as a hydrogen transfer agent. If an unsaturated compound such as sodium phenyl isocrotonate is added to a solution of hypophosphite, then sodium phosphite is obtained on the one hand and sodium phenyl butyrate on the other.

The oxidation of alcohol by air or oxygen is accelerated by active nickel. Alcoholic suspensions, on standing in the presence of air, are oxidized slowly with the formation of aldehydes and acids. If the suspensions are shaken, aldehydes or ketones can be detected after a few minutes. The oxidation is accelerated to the point of ignition in the presence of oxygen.

3. Raney Nickel as Dehydrogenation Catalyst

In connection with oxidation studies a few experiments describe Raney metals as dehydrogenation catalysts. Paul[26] and Palfray and Sabatay[27] have studied the behavior of nickel. According to them the dehydrogenation action is apparent with alcohols at relatively low temperatures. Isopropyl alcohol is dehydrogenated at its boiling point. The action is too slight to be of value for preparative purposes. The yields, without ever becoming quantitative, are greater with alcohols of higher boiling points. Decreasing activity of the catalyst is not responsible for the incomplete conversion, because used catalyst shows undiminished activity in repeated experiments. Paul believed that the dehydrogenating action stops because the aldehydes and ketones which are formed, owing to their unsaturated structure, are more strongly absorbed by Raney nickel than the alcohols. This assumption is supported by the observation that ethylene derivatives slow down the dehydrogenation of alcohols and acetylene compounds stop the action completely. This explanation is in agreement with the proposal of Schwab and Zorn[5] who assume that the points of activity in Raney nickel are not on the surface but, instead, within the crystals. The catalyst is clogged during dehydrogenation by absorbed reduction product. Conversely, the assumption of active points within the catalyst explain the activity as a reducing catalyst. The hydrogen which can diffuse rapidly is always present in greatest concentration in the neighborhood of the active points.

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[26] Paul, *Bull. soc. chim.*, **5**, 1592 (1938); *Compt. rend.*, **208**, 1319 (1939).
[27] Palfray and Sabatay, *Compt. rend.*, **208**, 109 (1939).

Dehydrogenation of alcohols by Raney nickel is not the only reaction which occurs. It is accompanied by reduction which converts part of the alcohol to hydrocarbons, or in the case of unsaturated alcohols reduces the double bond. At 140°C. cinnamic alcohol forms hydrocinnamaldehyde, hydrocinnamic alcohol, propylbenzene, and propenylbenzene. Furfuryl alcohol gives a 22% yield of methylfuran. Allyl alcohol becomes heated spontaneously to its boiling point on introduction of Raney nickel and yields 66% of propionaldehyde and 16% methylethylacrolein. The latter is formed by aldol condensation of part of the propionaldehyde.

Raney nickel does not seem to have been studied for dehydrogenations in the gas phase. Raney copper, Raney cobalt, and Raney nickel-copper (containing 35% copper) have proved to be good dehydrogenation catalysts at higher temperatures. They are superior to reduced copper for this purpose. Raney copper starts to reduce alcohols at 170°C. The reaction proceeds very well with primary alcohols at about 300°C. and with secondry alcohols at 250°C. Raney cobalt is even more reactive, starting to cleave hydrogen at 100° to 175°C. Primary alcohols are dehydrogenated well by Raney cobalt at 200° to 250°C. and secondary alcohols with fair speed at 200°C.

Active nickel-copper has the same speed as active cobalt and, regardless of its nickel content, does not induce side reactions.

The observation of Delépine and Horeau[28] that Raney nickel can accelerate or induce the Cannizzaro reaction belongs in the class of dehydrogenation studies. The Cannizzaro reaction is the conversion of certain aldehydes to the corresponding alcohols and acids in the presence of alkali. Only certain aldehydes undergo this reaction, the classical example being benzaldehyde. Benzaldehyde undergoes the reaction so fast that it is hardly influenced at all by Raney nickel. In the case of formaldehyde the conversion is a slow one. A 3% solution of formaldehyde is 50% disproportionated after 30 hours to methyl alcohol and formic acid. In the presence of Raney nickel the conversion is almost 100% complete after $^1/_2$ to

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[28] Delépine and Horeau, *Bull. soc. chim.*, 4, 1524 (1937).

3 hours, depending on the amount of catalyst which is added. In the presence of alkali alone, butyraldehyde undergoes an aldol condensation; in the presence of alkali and Raney nickel the Cannizzaro reaction takes place. The monosaccharides behave as does butyraldehyde; only in the presence of Raney nickel are they converted quantitatively to the corresponding alcohols and acids. The Cannizzaro reaction can be induced without alkali in the presence of sufficient amounts of Raney nickel.[29]

Platinum behaves like Raney nickel. The Cannizzaro reaction is avoided by the addition of an easily reduced substance. These added substances are hydrogenated directly; *e.g.*, a sugar is quantitatively dehydrogenated to the corresponding acid. On the basis of their studies Delépine and Horeau were able to give further experimental support to Wieland's theory of oxidation of aldehydes to acids. According to this theory the oxidation is really a dehydrogenation of the hydrated form of aldehyde. In the presence of a suitable hydrogen acceptor the dehydrogenation gives carboxylic acids. In the absence of an acceptor the Cannizzaro reaction occurs, with the aldehyde itself assuming the role of hydrogen acceptor.

4. Special Reactions of Raney Nickel

In the reduction of 2,6-dimethyldihydropyran-3-carboxylic acid, which is obtained by oxidation of the dimeric form of crotonaldehyde, Delépine and Horeau[30] observed the migration of the double bond in this acid under the influence of Raney nickel. In addition to the expected tetrahydropyrancarboxylic acid, they found 10% of a dihydropyrancarboxylic acid which was isomeric with the starting material. The acid was a result of a shift in the double bond from position 3,4 to 2,3. The dihydro acid could be isolated because it was not reduced further under the conditions which were employed. This rearrangement took place slowly in the cold, being 21% complete after 6 hours, and rapidly in the heat, being 60% complete at 100°C. after 1 hour. Similar types of rearrangement effects have been observed during reductions with other catalysts. We need only to recall the shift of the double bond during the hardening of fats and the rearrangements brought about in the terpene series by palladium.

In the reduction of aldoximes with Raney nickel Paul[31] has observed the formation of small amounts of acid amides as a result of the rearrangement of the aldoximes. This rearrangement is induced by Raney nickel and takes place even in the cold. A few oximes become appreciably warmer on introduction of Raney nickel and show partial rearrangement. The rearrangement is complete after a few hours in boiling alcohol or at water bath temperature. The yields of acid amides are generally 75 to 100%. As would be expected from the exothermic nature of the reactions, they are violent at higher temperatures. The role played by the Raney nickel in these rearrangements has not been established clearly. On introduction of nickel the oximes or their solutions become colored a deep red. A small amount of the catalyst dissolves. The dissolved metal is able to promote the rearrangement or carry it to completion after separation of the undissolved Raney nickel. If, for example, the red residue obtained by treatment of 100 g. of furfural oxime with Raney nickel is ashed, 0.5 g. of metal oxide is found. Iron and aluminum as well as nickel are contained in the oxide residue. The proportion of iron and aluminum is far greater than their relative concentrations in Raney nickel. The same rearrangement effect has been observed previously only with reduced copper. However, in the case of copper, the rearrangement temperature is about 200°C. and the yields are only about 6%. While copper is able to induce the rearrangement of ketoximes as well as aldoximes, Raney nickel works only with aldoximes.

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[29] Delépine and Hanefraaff, *Bull. soc. chim.*, 4, 2091 (1937).
[30] Delépine and Horeau, *Bull. soc. chim.*, 5, 339 (1938).
[31] Paul, *Bull. soc. chim.*, 4, 1115 (1937).

Raney nickel has a very strong affinity for sulfur, both organic and inorganic. The action of Raney nickel on sulfur compounds is not catalytic. It removes 1 atom of sulfur in the cold from sodium thiosulfate[32] with the formation of sodium sulfite, a reaction which takes place in the presence of copper only at temperatures exceeding 100°C. Sulfur is completely removed from sodium sulfite at 100°C. The sulfur is only partially removed from antimony sulfide and completely removed from tin sulfide. Sulfur is removed from organic compounds in aqueous or alcoholic solution, usually even in the cold.[33] Some reduction and hydrogen evolution are observed as side reactions. A list of some sulfur compounds and their degradation products are given below:

Carbon disulfide	Methane
Thiourea	CH_4, NH_3, CH_3NH_2
Benzylthiourea	Toluene, NH_3, CH_3NH_2
$HSCH_2COOH$ $(SCH_2COOH)_2$	CH_3COOH
$HSCH_2CH_2SH$	CH_3CH_3
CH_3COSH	CH_3COOH in water CH_3CHO in alcohol

The removal of sulfur from organic compounds under the influence of Raney nickel has also been the object of recent studies by Mozingo and co-workers.[34] They showed with a wide variety of compounds that an active Raney nickel catalyst in the presence of a solvent removed either reduced or oxidized sulfur by cleavage at a moderate temperature from the remainder of the organic molecule.

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[32] Aubry, *Bull. soc. chim.*, **5**, 1336 (1938).

[33] Bougault, Cattelain, and Chabrier, *Compt. rend.*, **208**, 657 (1939); *Bull. soc. chim.*, **6**, 34 (1939).

Sulfur is split so easily that a quantitative method for the determination of organic sulfur could be based on the reactivity of Raney nickel. The hydrogen sulfide liberated by decomposition of the nickel sulfide could be determined. The nickel sulfide formed in these reactions differs from normal nickel sulfide by being decomposed easily with dilute acids.

IV. REDUCTIONS WITH RANEY CATALYSTS

It is the unanimous opinion of investigators who have studied reductions with Raney metals extensively that these catalysts are superior to previous reduction catalysts in their activity. Because of this activity, Raney metals permit the use of milder reaction conditions, especially lower temperatures, in bringing about reductions. Their use has brought about the reduction of many unstable substances, which formerly were hampered by side reactions and cleavages. Conversely, they have permitted the use of customary reaction conditions with stable compounds and cut down the time required for their reduction to a fraction of that previously necessary. In the absence of extensive comparative data and systematic comparative experiments, it is impossible to determine whether the increased activity of Raney metals is equally apparent with all classes of compounds. For the same reason it is difficult to make an objective evaluation of this class of compounds and its advantages, even if one bases his comparisons on the abundance of data which have been compiled in numerous publications.

In the last analysis a particular judgment must be based upon particular experiments. In order to do this it is necessary to make assumptions just as one would do with the previously available catalysts. It is necessary to have an intimate knowledge of the properties and peculiarities of the catalysts. One must take into consideration the availability and range of applicability of the catalyst and, finally, the properties of the compounds to be hydrogenated and of the hydrogenation products.

The range of applicability of the individual metals in their active form appears, so far as has been determined, to be about the same as that in which individual metals have been applied previously. In many reductions nickel has been substituted for the noble metals, for palladium especially. On further study it is conceivable that cobalt will be able to take the place of Raney nickel. In the reduction of carboxylic acids and carboesters to alcohols or of carboxylic amides to amines, for which other nickel catalysts have not been particularly good, Raney nickel, too, has been applied only with moderate success. Inasmuch as such attempts have not been completely negative, it is entirely possible that an active metal or active pair may be found which will permit such reductions to be carried through with the same degree of success as has been shown up to now only with chromite catalyst.

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[34] Mozingo, Wolf, Harris, and Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

In order to give a better general view of the subject, the data accumulated with Raney catalysts have been assembled on the following pages not according to the class of compounds which have been reduced, but, instead, according to the individual metals which have been used as reducing catalysts.

1. Raney Iron

Of the three metals, iron, nickel, and cobalt, which are in Group 8 of the periodic system, iron has the least power to transfer hydrogen. This power is not changed appreciably even in active iron prepared by way of an alloy. Paul and Hilly[35] were the first to study its use widely. According to them active iron has the power to reduce carbonyl, nitrile, and nitro groups, as well as ethylene bonds at 100 atmospheres and at temperatures around 100°C. On the other hand, acetylene bonds are attacked rather easily and reduced simply to double bonds. The reduction proceeds quantitatively and without side reactions regardless of the position of the triple bond in the chain. The pressures which are used lie between 50 and 75 atmospheres and the temperatures between 100° and 135°C.

2. Raney Copper

Our knowledge of the behavior of active copper is just as full of gaps as that on active iron. Apparently a single publication by Faucounau is the only material available on active copper. Faucounau limited his studies to a few simple unsaturated and carbonyl compounds. These experiments were carried out uniformly, 10% of catalyst and an initial pressure of 100 atmospheres being employed. He studied only two acetylene compounds, phenylacetylene and 1-heptine. Of these phenylacetylene decomposed explosively in the presence of fresh catalyst at 80°C. Resins were obtained with an older catalyst. At 100°C. heptine gave a mixture consisting of 60% heptane as well as diheptene and triheptene. In the case of limonene only the double bond of the isopropylene group was reduced at 200°C. The double bond of the ring was not touched. A 90% yield of carvomenthene was obtained. Treated in the same way cyclohexene and pinene were not attacked. On the other hand, allyl alcohol was reduced quantitatively to propyl alcohol below 100°C. According to these results Raney copper behaved like reduced copper with compounds in the gas phase, in that only terminal double bonds were reduced. Ipatieff was able to reduce pinene and camphene to saturated compounds only by using pressure in the liquid phase.

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[35] Paul and Hilly, *Compt. rend.*, **206**, 608 (1938); *Bull. soc. chim.*, **6**, 218 (1939).

Although Raney copper does not show any outstanding merit in the compounds mentioned up to now, it does show an appreciably greater activity than reduced copper for the reduction of carbonyl compounds. Reduced copper attacks aldehydes and ketones slowly only above 200°C. Because of the dehydrogenating action of copper these compounds are converted incompletely into alcohols. It is claimed that acetone can be converted to a 65% yield of isopropyl alcohol only at temperatures starting in the range of 280° to 300°C. When active copper is employed, the aldehydes give 70 to 98% yields of alcohols at 125° to 150°C. Ketones can be reduced with equally good yields at 95° to 125°C. It is possible that active copper may attain a preparative importance in this field, especially for the reduction of unstable carbonyl compounds, because copper does not show the same degree of cleavage and condensing action as does nickel.

Inasmuch as reduced copper is suitable for the reduction of other compounds, such as nitro substances, nitriles, oximes, acid amides, carboxylic acids, and their esters, an increase in the scope of Faucounau's investigations with active copper would be greatly welcomed.

3. Raney Cobalt

As a reducing catalyst cobalt is similar to nickel, but, except for special purposes, it has found practically no application because of its lesser activity. The only available publications are those of Sabatier and Senderens who studied reductions in the gas phase. They ascribe to cobalt an activity which is similar to but weaker than that of nickel. They have also reported that this activity declines rapidly. However, no comparisons may be made between the results of Sabatier and those reported on Raney cobalt. The latter have been obtained exclusively from pressure reductions. Faucounau carried out his experiments[20] on a parallel with those of active copper, by always starting with a hydrogen pressure of 100 atmospheres. A comparison with ethylene compounds revealed cobalt to be the more active catalyst. Cobalt caused hydrogen addition to terminal double bonds as well as to those in the rings. The temperatures required were 100°C. for allyl alcohol, 110°C. for cyclohexene, and 140° to 150° C. for pinene. At 175°C. limonene gave a mixture which contained predominantly carvomenthene and paramenthane. The former had resulted from reduction of the external double bond and the latter from reduction of both double bonds. At 200°C. the benzene nucleus was also reduced. With carbonyl compounds, Raney cobalt showed an activity similar to that of copper. These compounds were reduced slightly above 100°C., acetone giving a quantitative yield of isopropyl alcohol at 100° to 110°C. and benzaldehyde an 85% yield of benzyl alcohol.

The published results of Faucounau are probably subject to correction, because Dupont[8] showed that the cobalt used by Faucounau was contaminated. After purifying the catalyst, Dupont was able to reduce limonene at 149°C. and 25 atmospheres. In the presence of Raney nickel limonene is reduced rather gradually at room temperature and normal pressure. To carry out reductions with active cobalt under normal conditions has little practical value.

The United States Patent 2,166,183 granted to du Pont refers to a field in which active cobalt has a practical value. du Pont uses cobalt for the reduction of dinitriles, exceptionally good yields of primary diamines being obtained. For example, 1,6-diaminohexane, 1,7-diaminoheptane, and so on up to 1,10-diaminodecane were obtained from the corresponding dinitriles in approximately 97% yields at 120°C. and 75 to 150 atmospheres, in the presence of ammonia. Even without ammonia 87% yields of diamines are obtained. These yields cannot be realized with nickel, because this metal, in general, favors the formation of secondary and tertiary amines during the reduction of nitriles. A few pure aromatic nitriles are exceptions. To obtain good yields of primary amines with nickel it is necessary to carry out the reductions in the presence of ammonia or ammonia salts.[36] Raney cobalt is preferable to nickel quite generally in reductions in which primary amino groups are desired. This is true in the reduction of nitriles, oximes, and in the catalytic amidation of carbonyl compounds. Reduced cobalt is not active enough for these purposes.

4. Raney Nickel

There is probably no single class of unsaturated compounds whose reduction has not been tested with Raney nickel. It is difficult to make a survey of the data published on the use of Raney nickel as a reduction catalyst, because of the unsatisfactory references to Raney nickel as an item in the indices of chemical publications. Often references are completely missing in the reference manuals. In addition to those publications which are particularly concerned with reductions in which Raney nickel is employed, there are innumerable individual publications mentioning the use of this catalyst for preparative purposes. It is possible to obtain a survey of American work from Homer Adkins' book, *Reactions of*

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[36] Mignonac, British Patent, 282,083.

Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts, published in 1937.

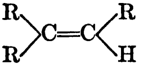
5. Reduction of Ethylene Bonds

"A Raney catalyst makes it possible to carry out reductions at temperatures and pressures which are essentially lower than those which are necessary with a catalyst prepared by the Sabatier method." This is the opinion of Dupont[37] in a publication on the reduction of double bonds by means of Raney nickel. With Campbell and O'Connor[38] he places Raney nickel on a par with palladium for suitability in partial addition of hydrogen.

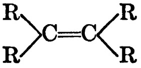
Ethylene bonds can be reduced at normal temperatures and pressures. Terminal double bonds are reduced at a constant speed in compounds such as *n*-heptene, styrene, *1*-phenylpropylene, safrole, and eugenol. If the double bond is secondary in an open chain, or in a ring, as typified by 2-octene, cinnamic alcohol, and cyclohexene, then the reduction proceeds at a slower rate. In general, the absorption of hydrogen is slower than with primary double bonds; this is illustrated by safrole and isosafrole, eugenol and isoeugenol.

A tertiary double bond, is reduced in the same way as asymmetric disubstituted ethylenes.

If the groups are arranged as follows, no addition is likely to occur.



and



If two double bonds are present in the compound, they activate each other. It is not possible to carry out a selective reduction. If one of the ethylene groups is tertiary, it is not attacked. In limonene the isopropylidene group is reduced; carvomenthene is formed. If two tertiary double bonds are present within the molecule, one may be reduced.

Δ^3-Menthene is obtained from terpine. Besides, the double bonds in terpines are conjugated. The partial reduction of conjugated double bonds is ambiguous because either 1,4 or 1,2 addition can take place.

We may choose as examples myrcene,[39] a hydrocarbon from lemongrass oil, and alloocimene[40] which is obtained by the pyrolytic cleavage of pinene.

Both compounds contain three double bonds, of which two are conjugated in myrcene and all three in alloocimene. Under normal conditions

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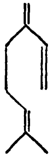
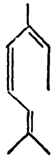
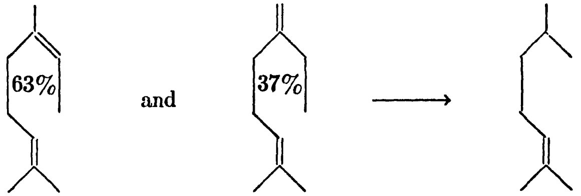
[37] Dupont, *Bull. soc. chim.*, **3**, 1021 (1936).
[38] Campbell and O'Connor, *J. Am. Chem. Soc.*, **61**, 2897 (1939).
[39] Dupont and Desreux, *Bull. soc. chim.*, **4**, 422 (1937).
[40] Dupont, Dulon, Desreux, and Picoux, *Bull. soc. chim.*, **5**, 322 (1938).


Myrcene


Alloocimene

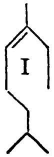
myrcene takes up somewhat more than 1.3 moles of hydrogen. One molecule of hydrogen is absorbed at a uniform speed during the first step. Both of the following dienes are formed concurrently as a result of 1,4 and 1,2 addition:

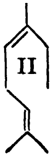


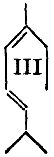
Methylgeraniol Dihydromyrcene 2,6-Dimethyl-2-octene

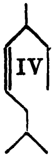
Only the second of these compounds is reduced further to 2,6-dimethyl-2-octene. The addition of hydrogen takes place similarly with palladium, the 1,4 addition being even more strongly favored.

The addition of hydrogen takes place differently in the case of alloocimene. 2 moles of hydrogen are absorbed very rapidly by this hydrocarbon, 2,6-dimethyl-5-octene (I), a small amount of 2,6-dimethyl-6-octene being formed. Inasmuch as a mixture of hydrocarbons is obtained after the absorption of 1 mole of hydrogen, in which mixture much starting material remains, no correct conclusions can be drawn on the course of the reaction. A primary addition at the 4,7 position gives the diene, II, which, like the isomeric methylgeraniol, can scarcely be reduced any further with Raney nickel. An addition to the end of the system gives the diene, III, which should give a mixture of the two steric isomeric ethylene hydrocarbons, IV, on further reduction.









In unsaturated alcohols the position of the hydroxyl group has no apparent influence on the double bonds. Cinnamic alcohol and allyl alcohol add hydrogen under normal conditions. Smith and co-workers[41] have used Raney nickel for preparative purposes in the cases of dihydrocitronellol and hexahydrofarnesol. On the one hand they started with citronellol and on the other with farnesol. They found that citronellol gave a quantitative yield of the dihydro derivative at 80° to 125°C. and 150 atmospheres. Under these conditions geraniol absorbed only 2 atoms of hydrogen. 2 more atoms were absorbed only at 200°C. and 185 atmospheres, giving a 90% yield of product. Farnesol behaved like geraniol, giving a 90% yield of hexahydrofarnesol. These investigators assumed that the hydroxyl group in geraniol and farnesol hindered the reduction of the adjoining double bond. This assumption was not borne out, because Dupont[42] was able to reduce geraniol to citronellol in the cold with Raney nickel. It was formerly thought to be unreducible under these conditions. The isomer, linalool, behaved analogously, only the terminal double bond being reduced.

Double bonds are activated by carbonyl groups which are not too far away. However, if a primary or secondary double bond is in conjugation with a carbonyl group, hydrogen is added slowly. The carbonyl group is also attacked without appreciable change in the speed of the reduction. For example, cinnamic aldehyde gives dihydrocinnamaldehyde, dihydrocinnamic alcohol, and unchanged starting material when 1 mole of hydrogen is used.[43] Benzalacetone behaves similarly, but its double bond is more difficult to reduce. If a tertiary double bond is conjugated with a carbonyl group, the reduction is accelerated and goes selectively. With 1 mole of hydrogen, citral gives a mixture of unchanged material, citronellal and citronellol. 2 moles of hydrogen give citronellol exclusively. The activating influence of a conjugated carbonyl group is demonstrated by the reduction of pulegenone and camphorone.[44]

Although the double bond of pulegenone is secondary-tertiary and that of camphorone ditertiary, both double bonds are reduced under normal conditions, that of camphorone being reduced more slowly. Ionone is an example of a carbonyl compound containing two conjugated double bonds. This compound was reduced by Kandel[45] at 150 atmospheres and progressively higher temperatures. At 65°C. he obtained dihydroionone as a result of the reduction of the external double bond. At 90°C. he obtained dihydroionol, without the double bond in the ring being touched. It is questionable whether these conditions are necessary for the reaction, because Ruzicka[46] has been able to carry the reduction through to dihydroionone at normal pressure in the presence of a nickel catalyst which he does not describe more definitely. In general, double bonds of unsaturated carboxylic acids are reduced under normal conditions. This is shown by the behavior of undecylenic, maleic, fumaric, and oleic acids. Here, too, hydrogen is added more slowly to secondary double bonds than to primary ones. In order to prepare alkylated acetoacetic, malonic, and succinic esters Wojcik[47] reduced a series of aldehyde condensation products of the above esters at room temperature and at pressures between 1 and 200 atmospheres, obtaining the alkyl esters in yields exceeding 90%. Allen and coworkers[48] reduced a few unsaturated acids at high pressure in the form of their alkali salts. An excess of alkali proved beneficial for the reduction of these salts. It may be mentioned here that the author also studied the reduction of alkali salts of hydroxy acids at high pressures and temperatures up to 250°C. Under these conditions α- and γ-hydroxy acids were unchanged. The hydroxyl group was split from β-hydroxy acids. Of the hydroxydicarboxylic acids, malic acid gave a 93% yield of succinic acid. At 235°C. tartaric acid lost one hydroxyl group and one carboxyl group, giving a yield of lactic acid.

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[41] Smith, Ungnade, Austin, Prichard, and Opie, *J. Org. Chem.*, **4**, 334 (1939).

[42] Dupont, *Bull. soc. chim.*, **4**, 2016 (1937).

[43] Delépine and Hanefraaff, *Bull. soc. chim.*, **4**, 2087 (1937).

[44] Calas, *Bull. soc. chim.*, **6**, 1391 (1939).

[45] Kandel, *Compt. rend.*, **205**, 994 (1937).

Ruggli and Businger[49] reduced the potassium salt of cyanoacetic acid in an autoclave with Raney nickel in a saturated ammoniacal solution of methanol at 80°C. and 100 atmospheres, obtaining a 75% yield of β-alanine.

For the reduction of fats Bag and co-workers[13] used a nickel-aluminum alloy from which 8% of the aluminum had been removed. At normal pressure the catalyst reacted at about 100°C. Escourou[50] investigated extensively the reduction of fats under reduced pressures in the presence of Raney nickel, but we shall not describe this work in detail.

Partial reduction of sorbic and muconic acids[51] permits us to draw a few conclusions regarding the influence of carboxyl groups on double bonds. The results of these experiments which were carried out with Raney nickel (R-Ni), platinum, and palladium are tabulated on page 82.

With sorbic acid the addition takes place chiefly at the double bond which is not in conjugation with the carboxyl group. Addition to the double bond adjoining the carboxyl group and at the end of the conjugation is slight. Raney nickel is not far behind palladium in selective ac-

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[46] Ruzicka, *Helv. Chim. Acta*, **17**, 637 (1934).

[47] Wojcik, *J. Am. Chem. Soc.*, **56**, 2424 (1934).

[48] Allen, Wyatt, and Henze, *J. Am. Chem. Soc.*, **61**, 843 (1939).

[49] Ruggli and Businger, *Helv. Chim. Acta*, **25**, 35 (1942).

[50] Escourou, *Bull. soc. chim.*, **5**, 1184 (1938); **6**, 191 (1939); **6**, 360 (1939); **7**, 180 (1940).

[51] Farmer and Hughes, *J. Chem. Soc.*, **1934**, 1929.

Sorbic Acid, $CH_3\cdot CH{=}CH\cdot CH{=}CH\cdot COOH$

	Pt *per cent*	Pd *per cent*	R-Ni *per cent*
Starting material	44		4
α-Dihydro acid	7	68.5	83
β-Dihydro acid	5		?
γ-Dihydro acid		2.3	0.4
Capronic acid	44		3
Unseparated with β-dihydro acid		11.2	9.6

Muconic Acid, $HOOC{-}CH{=}CH{-}CH{=}CH{-}COOH$

	Pt *per cent*	Pd *per cent*	R-Ni *per cent*
Starting material	40.3	10.8	26.9
α-Dihydro acid	11.3	56.3	31.6
β-Dihydro acid	7.5	14.8	15.0
Adipic acid	40.3	10.8	26.9
Residue	7.3		

tion. With muconic acid, there is little tendency for selective addition because of the symmetrical molecule. However, it is apparent that the more selective the catalyst, the stronger is the tendency for 1,2 addition to occur. In this respect Raney nickel lies between palladium and platinum.

6. Reduction of Acetylene Bonds

Reduction of triple bond compounds in the presence of Raney nickel has not been studied extensively. Only Dupont[52] and Campbell and O'Connor[38] appear to have studied this problem. Both groups worked at room temperature, in so far as the exothermic course of the reaction would allow. Dupont, working at normal pressure, and Campbell, working at 3 to 4 atmospheres, obtained the same results.

Terminal acetylene bonds are reduced with great speed to ethane derivatives, without any noticeable decrease in the rate of absorption after the first mole of hydrogen has been absorbed. The reduction is not altogether selective, because if the reaction is stopped after the absorption of 1 mole of hydrogen and the products examined, as in the case of phenylacetylene, there still remains 15% of starting material and in the case of *n*-heptine, 5%. For preparative purposes this contamination is not very important, because the acetylenes can be separated readily from the ethylenes as salts.

If the acetylene bond is in a chain, hydrogen is absorbed at a constant rate until the ethylene bond is formed. Further reduction takes place at a slower rate, so that a curve of the hydrogen absorption shows a break.

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[52] Dupont, *Bull. soc. chim.*, **3**, 1030 (1936).

With asymmetric acetylenes such as 2-octine, 1-methoxy-2-octine. 1-carboxyalkyl-2-octine, and phenylmethylacetylene the rate of decrease is not as marked as with symmetrical dialkyl acetylenes. With symmetrical diphenylacetylene reduction stops after 1 mole of gas has been absorbed. In most cases the olefins can be obtained in a pure form if the reduction is stopped after the absorption of 1 mole of hydrogen. In general, *cis* forms of the olefins are obtained.

7. Reduction of Carbonyl Groups

Delépine and Horeau[17] published a study concerned specifically with the reduction of carbonyl compounds in the presence of Raney nickel. They started with the observation that pinonic acid, a ketocarboxylic acid, could be reduced successfully only if more alkali was used than that required for the formation of the neutral salt. They extended the study to the reduction of about forty different carbonyl compounds, by adding small amounts of alkali to each. Delépine had previously drawn attention to the beneficial influence of alkali on the course of reductions, but there was lacking a systematic evaluation of the observation, such as was made in the reduction of the carbonyl groups.

The observations of Delépine can be summarized as follows: Raney nickel can be used for the reduction of carbonyl compounds under normal conditions. The rate of hydrogen absorption differs greatly with the individual compounds. An activation of the nickel with small amounts of noble metals, such as platinum or palladium has little influence on the rate of reduction in the absence of alkali. If small amounts of alkali are added to carbonyl compounds, the rate of gas absorption is increased three- to four-fold; in some cases a ten-fold increase is noted. When Raney nickel has been activated by noble metals, the influence of alkali is even greater. Here, activation by the noble metal becomes apparent. It is difficult to give an explanation for the action of the alkali. An enolization, therefore an activation of the substance to be reduced, cannot be assumed, because the action occurs even with carbonyl compounds which cannot undergo enolization. Therefore, an activation of the catalyst itself must be involved. Foresti and Chiume[53] have attempted to explain this matter.

Undoubtedly the good results of Delépine are to be explained by his use of a completely fresh Raney nickel which had not lost any of its activity through age. Immediately before each experiment he decomposed an equivalent amount of alloy to obtain the required amount of nickel, this procedure requiring only a little time because of the small quantities with which he was concerned. Reichstein and Gätzi[54] used the same procedure to get very small amounts of nickel, in carrying out reductions with small quantities of substance. Delépine carried out his experiments with simple unsaturated ketones. He was able to demonstrate how the introduction of some sodium hydroxide renewed the reduction of the carbonyl group with great speed after the reduction had slowed down, following absorption of enough hydrogen for the double bonds. Carbonyl groups flanked on each side by branched chains are not attacked under normal conditions. The same effect is shown by cyclic ketones which are substituted by alkyl groups on 2 adjacent carbon atoms, such as in fenchone, pulegnone, and camphorone. The carbonyl groups in these compounds can be reduced in the presence of platinum. They are reduced all the way to hydrocarbons instead of to the alcohols. On the other hand, cyclohexanone, camphor, and cholestanone can be reduced. Aromatic ketones such as benzophenone and fluorenone give carbinols; diketones such as acetylacetone and keto alcohols such as benzil, benzoin and one of the pinanolones give glycols; keto acids and esters, such as acetoacetic ester, acetylsuccinic acid ester, levulinic acid, and mesoxalic ester give the corresponding hydroxy acids or their esters.

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[53] Foresti and Chiume, *Gazz. chim. ital.*, 67, 408 (1937).

With aldehydes, the results are mostly good. In activating these compounds with alkali it must be borne in mind that the Canizzaro reaction and condensations can occur during the reversible reaction. The same is true in the reduction of sugar. To learn the particulars for carrying out the reductions, it is best to refer to the original work.

We shall only mention in passing the behavior of the reduction products of carbonyl compounds of primary and secondary alcohols during reduction in the presence of Raney nickel at high temperatures. With secondary alcohols the carbon-oxygen bond is broken above 200°C., the corresponding hydrocarbons being formed. The same cleavage occurs at appreciably lower temperatures with primary alcohols which have a benzene or pyrrole nucleus in the α position, whereas the furan and pyridine rings have much less loosening effect on the C—O bond. In other primary alcohols a cleavage of the hydrocarbon chain occurs between the first and second carbon atoms. The next lower hydrocarbon is formed according to the following equation.

$$R{-}CH_2{-}OH + 2H_2 \longrightarrow RH + CH_4 + H_2O$$

A cleavage of methanol is probably to be assumed as the first step and this is then reduced further to methane. With diprimary glycols, hydrocarbons which have 2 carbon atoms less are formed. With primary-secondary glycols the hydroxymethyl group is split and the secondary hydroxyl group can also be split.[55] The following compounds are formed at 250°C.

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[54] Reichstein and Gätzi, *Helv. Chim. Acta*, 21, 1497 (1938).

1-Tetradecanol	90%	tridecane
1-Octadecanol	80%	heptadecane
3-Cyclohexyl-1-propanol	80%	ethylcyclohexane
1,10-Decanediol	90%	octane
1,4-Heptanediol	66%	3-hexanol
1,12-Octadecanediol	75%	heptadecane

Reichstein and Gätzi[54] used Raney nickel for preparative purposes, by reducing a keto alcohol of the cyclopentenophenanthrene series to the glycol.

Shriner and Teeters[56] mention the use of Raney nickel in the reduction of 1-keto-2-(*p*-dialkylaminobenzal)tetrahydronaphthalenes to 1-hydroxy-2-(*p*-dialkylaminobenzyl)tetrahydronaphthalenes at usual temperatures and 3 atmospheres. With platinum, the double bond, but not the keto group, was reduced.

The reduction of *N*-acetyldiacetoneamine[57] has been cited as a further example of the reduction of an amino ketone with Raney nickel. 1 mole of hydrogen was absorbed under relatively severe conditions (100 to 200 atmospheres, 160° to 170°C.) with the formation of acetyl amino alcohol. The alcohol itself was formed only in poor yield, but the oxazine formed by cleavage of water was isolated in an 80% yield.

Stutsman and Adkins[58] have carried out reductions of 1,3-diketones of the general formula $CH_3CO—CH_2—CO—R$ in the presence of Raney nickel. R stands for the alkyl group from CH_3 to C_4H_9 in normal and branched chains. These compounds are reduced to the glycols in yields of 80 to 94% at 100° to 125°C. and 100 atmospheres. The reduction of a single keto group to the ketols is more difficult. Although the carbonyl group adjacent to the CH_3 is attacked first, it is not possible to detect any change in the rate of the reaction when the second carbonyl starts to be attacked. The instructions are to stop the reduction after 1 mole of hydrogen has been absorbed. The yields are fair, rising from 35% in the case of the methyl derivative to 66% with *n*-butyl and 70% with *t*-butyl groups. The yields were increased by 4% with methyl, 20% with *sec*-butyl, and 17% with *t*-butyl derivatives when the reaction conditions were modified in such a way that the pressure vessel was filled first to 100 atmospheres with nitrogen and then enough hydrogen was introduced to take the reduction half way; that is, to the ketol. The reduction was carried out until the partial pressure of the hydrogen had disappeared. Unsaturated ketones were formed from the ketols by loss of water and these were then reduced at 30° to 40°C. and 100 atmospheres to the saturated ketones. 1,3-Diketones were not always reduced as smoothly as these simple examples.[59] In addition to ketols and glycols, different types of cleavages took place. Depending on the constitution of the individual compound, these by-products were formed in considerable amounts.

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[55] Adkins and Wojcik, *J. Am. Chem. Soc.*, **55**, 1293 (1933). Adkins and Burdick, *J. Am. Chem. Soc.*, **56**, 438 (1934).

[56] Shriner and Teeters, *J. Am. Chem. Soc.*, **60**, 936 (1938).

[57] Smith and Adkins, *J. Am. Chem. Soc.*, **60**, 408 (1938).

[58] Stutsman and Adkins, *J. Am. Chem. Soc.*, **61**, 3303 (1939).

Diketene is converted to butyrolactone in the presence of Raney nickel.[60]

Even at relatively low temperatures carbon dioxide is reduced to formic acid in the presence of amines. Formates of the bases result at 80° to 100°C. and the formyl derivatives are obtained at about 150°C.[61]

8. Introduction of Amino Groups

The majority of methods which are available for the introduction of amino groups into organic compounds involve intermediate products, the reduction of which produces the amines. These reductions can be carried out by chemical methods as well as by catalytic methods with molecular hydrogen. The latter methods have the advantage that no foreign substances except solvent are present in the reaction product. As a result, the end-products can be isolated in pure form by simple methods. The reduction of nitro and nitroso compounds, oximes, azines, nitriles, and imino compounds, as well as the direct conversion of carbonyl compounds to amines by the method of Mignonac, belong to this classification.

Nitro and nitroso groups can be reduced readily to the amino groups in the presence of the usual nickel catalysts. Simple nitro compounds can generally be reduced very rapidly and smoothly under normal conditions in the presence of Raney catalysts. During the course of the exothermic reaction the temperature may rise by 100°C. More vigorous reaction conditions are necessary with complex or difficultly soluble nitro compounds. Quelet and Ducasse[62] reduced 3-nitro-4-methoxybenzyl alcohol, its acetate, and 3-nitro-4-methoxybenzaldehyde quantitatively to the corresponding amino alcohols. Chemical reduction methods are said to fail with these compounds. Because of its low solubility 3,3′-dinitro-4,4′-dimethoxydiphenylmethane required a temperature of 110°C. in alcohol for reduction to the diamino compound. Voris and Spoerri[63] reduced 2,4,6-trinitro-*n*-xylene almost quantitatively to pure triamine at 90°C. and

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[59] Sprague and Adkins, *J. Am. Chem. Soc.*, **56**, 2669 (1934).
[60] Boese, *Ind. Eng. Chem.*, **32**, 16 (1940).
[61] Farlow and Adkins, *J. Am. Chem. Soc.*, **57**, 2222 (1935).
[62] Quelet and Ducasse, *Bull. soc. chim.*, **6**, 466 (1939).
[63] Voris and Spoerri, *J. Am. Chem. Soc.*, **60**, 935 (1938).

3 atmospheres. They used platinized Raney catalyst and rather high temperature and pressure because the third nitro group is reduced with difficulty.

In the course of their study of benzodipyridine, Ruggli and Preiswerk[64] reduced nitro-*p*-phenylenediacrylic acids at room temperature to the aminodiacrylic acids. At 75°C. hydrocarbostyril-7-propionic acid was formed as a result of concurrent ring closure. The 6-nitro and 6,8-dinitro derivatives were also reduced with ring closure to 1,5-anthrazoline or 4,5-phenanthroline derivatives.

o,o'-Dinitrodesoxybenzoin produces *o,o'*-diaminodiphenylethane and 2-(*o*-aminophenyl)indole[65] simultaneously. Stevinson and Hamilton[66] reduced nitroarylarsonic acids to aminoarsonic acids.

A good example of selective reduction in the presence of Raney nickel has been furnished by Blout and Silverman.[67] They reduced alcoholic suspensions of nitrocinnamic acids and esters readily at 20° to 30°C. and 2 to 3 atmospheres to the corresponding aminocinnamic acids and esters in 75 to 95% yields. With *o*-nitro compounds further reduction gave hydrocarbostyril.

Catalytic reduction of aliphatic nitro compounds has become of interest since the successful direct nitration of aliphatic hydrocarbons, and since the nitro alcohols have also become readily available compounds. Johnson and Degering[68] reduced a series of nitro paraffins in alcoholic solution at 40° to 50°C. and pressures up to 110 atmospheres. They used Raney nickel, because other catalysts gave unsatisfactory yields. The amines were obtained in yields of 82 to 94%. The yields were improved somewhat by the introduction of small amounts of iron chloride in these reductions. Nitro glycols[69] were reduced under the same conditions as the nitro paraffins.

Finally we shall mention the reduction of nitroguanidines[70] which was carried out in the presence of platinum or Raney nickel; in the first step of the reduction nitrosoguanidines were formed (55 to 59% or 36 to 44%). Nitroguanidine was reduced to aminoguanidine in methanol with Raney nickel in a 75% yield. An 88% yield was obtained when nitrosoguanidine was used as the starting material. With rising temperature of reduction the yield dropped very rapidly. Methyl and ethyl nitroguanidine were reduced to nitroso compounds with nickel in neutral solution; they were reduced to the amino compounds with platinum in acid solution.

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[64] Ruggli and Preiswerk, *Helv. Chim. Acta*, 22, 478 (1939).

[65] Ruggli and Preiswerk, *Helv. Chim. Acta*, 22, 998 (1939).

[66] Stevinson and Hamilton, *J. Am. Chem. Soc.*, 57, 1298 (1935).

[67] Blout and Silverman, *J. Am. Chem. Soc.*, 66, 1442 (1944).

[68] Johnson and Degering, *J. Am. Chem. Soc.*, 61, 3194 (1939); U. S. Patent, 2,174, 498.

[69] U. S. Patent, 2,174,242.

[70] Lieber and Smith, *J. Am. Chem. Soc.*, 57, 2479 (1935); 59, 1834, 2287 (1937).

Reduction of oximes has often been employed for the preparation of aliphatic amines. This method has lost importance, because the direct catalytic amidation of carbonyl compounds by the method of Mignonac is suitable in most cases, making the indirect procedure by way of oxime unnecessary. However, there is a series of carbonyl compounds whose direct amidation gives some difficulties. In such cases the preparation of oximes as intermediate products must not be overlooked.

It is advantageous to use rather high temperature and pressure for carrying out the reduction of oximes. Raney nickel makes it possible to reduce aldoximes[71] under normal conditions. A mixture of primary and secondary amines results, the proportion of secondary amine often being considerable.

Reductions under high pressure are more satisfactory. In general ketoximes are reduced predominantly to primary amines, these being obtained in 80 to 95% yields at temperatures around 70°C. and pressures of about 50 atmospheres.

Smith and Adkins[72] likewise described the reduction of a series of oximes with Raney nickel, obtaining 45 to 64% yields of primary amines. These moderate yields are attributable to the high temperatures of 125° to 150°C. Use of these high temperatures is not understandable, because Adkins himself earlier had suggested 80°C. as the optimum temperature for the reduction of oximes with Raney nickel.[73]

In the reduction of nitriles to amines the temperature also has some influence on the course of the reaction and on the composition of the products. The results of Paty[74] who has obtained quantitative yields of ethylamine and phenethylamine by the reduction of acetonitrile and benzonitrile at ordinary temperatures in the presence of Raney nickel are to be regarded as unusually good. Generally speaking, it is necessary to reckon with the formation of 10 to 25% of secondary amines under these conditions Schwoegler and Adkins[75] report the ratio of primary to secondary amine as 3:1 to 2:1 at about 125°C. In exceptionally poor cases the ratios are reversed. Good yields of primary amines are obtained if the reductions are carried out in the presence of ammonia.[76] Schwoegler and Adkins have obtained 90 to 95% aminopentane and aminoheptane from *n*-butanenitrile and *n*-hexanenitrile at 125°C. and 150 atmospheres when they added 2 moles of ammonia to each mole of nitrile. Further details on the reduction of nitriles are to be found in publications by Smith and Adkins as well as by Barbier.[77] If the nitriles contain a second reactive group in a suitable position, ring closures can occur during the reductions. For example, pyrrolidone is formed from cyanopropionic esters[78] and piperidine from trimethylenenitrile.[79]

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[71] Paul, *Bull. soc. chim.*, 4, 1121 (1937).

[72] Smith and Adkins, *J. Am. Chem. Soc.*, 60, 660 (1938).

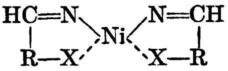
[73] Adkins, *Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts*, University of Wisconsin Press, Madison, 1937, p. 91. Winans and Adkins, *J. Am. Chem. Soc.*, 55, 2051 (1933).

[74] Paty, *Bull soc. chim.*, 5, 1276 (1938).

[75] Schwoegler and Adkins, *J. Am. Chem. Soc.*, 61, 3499 (1939). Adkins, *Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts*, University of Wisconsin Press, Madison, 1937, p. 54.

[76] Mignonac, British Patent, 282,083.

Raney nickel has a characteristic property of dissolving in the presence of ammonia and amines with the formation of complexes.[80] For this reason the reaction products separated from Raney nickel are more intensively colored than those obtained by the use of reduced nickel. Knowledge of this fact is probably attributable to Delépine[81] who noted a deep red to orange precipitate during the reduction of aminocyanopyrimidine with Raney nickel. This precipitate proved to be the nickel complex of an aminoaldimine. It had separated during the reduction of the nitrile because of its low solubility, and had escaped further reduction. Delépine and Jensen made a closer study of this phenomenon[82] by carrying out the reduction of the nitrile under such conditions that the aldimine became the main product. The following formula was ascribed to the nickel complex.



It is apparent that the nitriles must contain a group in a position which can participate in the complex formation. Up to now the course of the reduction has been observed with 2-methyl- and 2-ethyl-4-amino-5-cyanopyrimidine, *o*-aminobenzonitrile, and *o*-hydroxybenzonitrile. Related aldehydes can be obtained by hydrolysis of the complex salts.

Direct conversion of carbonyl groups into amino groups, which was observed first by Mignonac and studied intensively by Skita, has proved to be a useful contribution to the field of preparative chemistry. The reaction is essentially as follows: during the reduction of carbonyl groups in the presence of ammonia, primary, or secondary amines, the corresponding primary, secondary, or tertiary amines are formed. By this method it is not necessary to prepare and to isolate imines, hydroamides, or Schiff bases; they are formed as intermediates during the reaction. In general, direct amidation gives very good yields. Unfortunately, condensation products resulting from aldol condensations occur when this method is applied to aldehydes. Under such circumstances Raney catalyst may prove advantageous, permitting the use of lower temperatures. When ammonia is used as the base, primary and secondary amines are formed in varying amounts. If primary amines are desired as main products, the reaction conditions depend on the carbonyl compounds which are to be transformed. Important factors in this conversion are temperature and the ratio of ammonia to carbonyl compound.

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[77] Barbier, *Helv. Chim. Acta*, 23, 524 (1940).
[78] Winans and Adkins, *J. Am. Chem. Soc.*, 55, 4167 (1933).
[79] Paden and Adkins, *J. Am. Chem. Soc.*, 58, 2487 (1936).
[80] Grand Perrin, *Bull. soc. chim.*, 5, 112 (1938).
[81] Grand Perrin, *Bull. soc. chim.*, 5, 1539 (1938).
[82] Grand Perrin, *Bull. soc. chim.*, 6, 1663 (1939).

If Raney nickel is used, the required optimum temperatures, which are between 40° and 100°C., can be realized without the rate of reaction becoming too slow. When Schwoegler and Adkins[75] tried to convert carbonyl compounds to amines at 150°C., using a ratio of 0.5 mole of carbonyl compound to 0.7 mole of ammonia, they were able to obtain only fair yields of primary amines (19 to 72%). Fleury-Larsonneau[83] worked at 60° to 120°C. in preparing 2-aminobutane from methyl ethyl ketone, thereby obtaining 80% of primary amine. The yield would have been higher if a larger excess of ammonia had been chosen; because ketones, in general, require a greater excess of ammonia than aldehydes. Results with aromatic aldehydes were outstandingly good, 90% yields of primary amines being obtained at 75°C. in the presence of theoretical amounts of ammonia.[84] Direct amidation of ketones of the acetophenone type gave poor yields in the presence of Raney nickel. Schwoegler and Adkins obtained 19% of phenylethylamine from acetophenone. Cuturier,[85] without describing his reaction conditions, found the products to be 15% phenylethylamine, 40% phenylmethylcarbinol, and unchanged starting material.

The proximity of the benzene nucleus appears to decrease the reactivity of the carbonyl group under these conditions, because *o*- and *p*-methoxypropiophenone give only small yields of the amines, in addition to the alcohols. Benzyl methyl ketone, on the other hand, behaves normally and can be converted almost quantitatively to phenylisopropylamine. Phenyl ketones, having a free hydroxyl group ortho or meta to the carbonyl group, behave like benzyl methyl ketone. For example, *o*-hydroxy- and *m*-hydroxypropiophenone give good yields of the corresponding 2-(hydroxyphenyl)propylamines. These amines are surprisingly unstable and cannot be distilled; they hydrolyze on solution in aqueous hydrochloric acid. *p*-Hydroxypropiophenone behaves like acetophenone by giving a poor yield of amine.

Among the diketones Cuturier has reduced phenylpropanedione with methylamine in the presence of Raney nickel, obtaining a "rather good yield" of *dl*-ephedrine. Here we may note that Manske and Johnson, using platinum,[86] and Skita with his co-workers, using colloidal palladium[87] obtained yields of about 50%. On reducing acetonylacetone an ammonia, Schwoegler and Adkins obtained 28% of 2,5-dimethylpyrrolidine and 59% of 2,5-dimethylpyrrole. Acetylacetone was cleaved quantitatively to acetamide.

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[83] Fleury-Larsonneau, *Bull. soc. chim.*, 6, 1576 (1939).
[84] Winans, *J. Am. Chem. Soc.*, 61, 3566 (1939).
[85] Cuturier, *Compt. rend.*, 207, 345 (1938).

According to Mingoia,[88] Magidson and co-workers should use Raney nickel for the preparation of 1-diethylamino-4-aminopentane from 1-diethylamino-4-pentanone. The diamine is an intermediate for the preparation of the antimalarial, atabrine.

Emerson and Walters[89] carried out the alkylation of aniline with aldehydes and hydrogen, using both Raney nickel and platinum oxide. They preferred the Raney catalyst when they used sodium acetate as a condensing agent; they worked at room temperature and 3 atmospheres pressure. Using ratios of aniline to aldehyde of 1:2 up to 1:5, they obtained 47 to 65% yields of monoalkylanilines. Introducing alkyl chains varying in length from ethyl to amyl, they also obtained 10% of tertiary amines. With heptyl and benzyl radicals, tertiary amine was no longer a problem.

9. Reduction of Carboxyl Groups

Previously we have said that there is no useful Raney catalyst for the reduction of carboxyl groups. In a few instances when Raney nickel has been used a reduction has been observed. In general, the yields of reduction products are not good. The cyclic derivatives of a few dicarboxylic acids are exceptions. Apparently no reports are available on the behavior of free acids and normal esters. In the case of the cyclic esters, the lactones, a slight reaction takes place with formation of the cyclic ethers. Butyrolactone gives 9% of tetrahydrofuran at 200°C. and valerolactone gives 17% of methyltetrahydrofuran at the same temperature.[90] The lactone ring of octahydrocoumarin is reduced to hexahydrochroman.[91] It is claimed that a quantitative yield is obtained in this case if pure starting materials are used.

The yields obtained by the reduction of acid amides to amines are unsatisfactory. For example, the previously mentioned *N*-acetyl amino alcohol, when reduced at 170°C., gives about 30% yield of *N*-ethyl amino alcohol.

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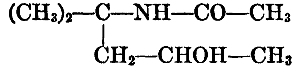
[86] Manske and Johnson, *J. Am. Chem. Soc.*, 51, 580 (1929).
[87] Skita, Keil, and Baesler, *Ber.*, 66, 858 (1933).
[88] Mingoia, *Ann. chim. anal. chim. appl.*, 30, 190 (1940).
[89] Emerson and Walters, *J. Am. Chem. Soc.*, 60, 2023 (1938).
[90] Wojcik and Adkins, *J. Am. Chem. Soc.*, 56, 2424 (1934).
[91] Benneville and Connor, *J. Am. Chem. Soc.*, 62, 283 (1940).



$$\begin{array}{l}(CH_3)_2\text{—}C\text{—}NH\text{—}CO\text{—}CH_3\\ \qquad\quad\ \ |\\ \qquad\quad CH_2\text{—}CHOH\text{—}CH_3\end{array}$$

D'Ianni and Adkins[92] applied Raney nickel, as well as copper-chromite, to the reduction of the piperidides of a few hydroxycarboxylic acids; with Raney nickel they obtained the fair yield of 15 to 34% of hydroxyalkylpiperidines.

The results obtained with cyclic derivatives of dicarboxylic acids are satisfactory. Phthalic anhydride[93] is reduced to a good yield of the phthalide. *N*-Substituted succinimides give up to 70% yields of *N*-substituted pyrrolidones, and substituted glutarimides give substituted piperidones.[79]

10. Reduction of Compounds Containing Halogen

The reduction of compounds containing halogen can have two objectives: replacement of the halogen atom by hydrogen, or reduction of some unsaturated group with retention of the halogen. Which of the two reactions will occur depends on the conditions of the reaction, especially on the temperature and on the nature of the halogen bond. Generally speaking, halogens are more firmly attached in the aromatic series of compounds than in the aliphatic ones. The mobility of the halogen decreases from iodine to chlorine.

Winans, Paty, and Anglade[94] studied the reduction of halogen compounds with Raney nickel. The data are not comprehensive enough for any general rules to be deduced. Double bonds to which are attached halogen atoms do not appear to be attacked. For example, 1-chloropropylene, symmetrical dichloroethylene, tetrachloroethylene, and chlorostyrene are not reduced. Benzyl chloride gives diphenylethane and resins. A 25% yield of xylenol ether is obtained at normal temperature and pressure from 2,4-di-(chloromethyl)anisole in alcohol, of alkali being present. Ether, formed by reaction with the solvent, occurs as a byproduct. When the reaction conditions are made more drastic, resins are formed. This is not surprising in view of the instability of aromatic chloromethyl groups in the presence of traces of heavy metal halides.

Chlorine occurring in aromatic compounds is stable up to temperatures of 150°C. Compounds such as 2,4-dinitrochlorobenzene, which gives a 91% yield of *m*-phenylenediamine at 40°C., are exceptions. Aromatic chloro hydrocarbons which contain ethylene or acetylene bonds in the side chain, nitro, nitroso, or azo groups, or substituents like CO—R, —CN,

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[92] D'Ianni and Adkins, *J. Am. Chem. Soc.*, **61**, 1675 (1939).

[93] U. S. Patent, 2,114,696.

[94] Winans, *J. Am. Chem. Soc.*, **61**, 3564 (1939). Paty, *Bull. soc. chim.*, **5**, 1276, 1600 (1939). Anglade, *Bull. soc. chim.*, **6**, 473 (1939).

—C═NOH, or —CH═NR behave otherwise. On reduction of these groups the compounds act as though they were chlorine-free.

Nearly quantitative yields of chloroaniline and dichloroaniline are derived from *o*-nitrochlorobenzene and nitro-2,5-dichlorobenzene. *p*-Chlorobenzonitrile gives a 64% yield of mono-*p*-chloro-benzylamine and 21% of the secondary amine; *o*-chlorobenzaldehyde in the presence of ammonia gives an 87% yield of *o*-chlorobenzylamine.

Bromo compounds do not react as smoothly as do chloro derivatives. Bromine may be removed during reduction from bromobenzene in the cold, in the presence of acid acceptors. Bromine is also removed from *p*-bromoanisole, although with somewhat greater difficulty. 2,4-Dibromoanisole loses first the bromine atom in position 2. Substituents such as —CH_2OH, —COOH, and —CH_2COOH in *p*-bromoanisole slow down the removal of halogen, but, nevertheless, the halogen-free compounds are obtained in good yields. On the other hand, *p*-nitrobromobenzene can be reduced to *p*-bromoaniline. The yield is 83% and lower than that obtained from chloroaniline; *o*-iodonitrobenzene gives only 23% of *o*-iodoaniline. *p*-Bromobenzophenone is reduced to *p*-bromobenzhydrol.

11. Reduction of Aromatic Compounds

According to Adkins, Raney nickel is inferior to nickel on kieselguhr for the reduction of aromatic nuclei. Too little data are available on the reduction of the benzene nucleus for any conclusive statements to be made on the suitability of Raney nickel. Actually, so far as comparative experiments have been made, Raney nickel is poorer for this purpose than nickel on kieselguhr, although the reaction temperatures are higher and the concentration of the catalyst is greater. For example, the quantitative reduction of benzene to cyclohexane, other things being equal, requires only 10 minutes at 125°C. with nickel on kieselguhr (5%), and 1 hour at 150°C. with Raney nickel (18%). The differences are not so great with toluene.[95] Poor yields are obtained with phenol ethers at high temperature (above 170°C.).[96] The yields of reduced phenol ethers vary with the constitution of the ethers, because cleavage of the ether link, as well as reduction, can occur. With benzyl ethers cleavage is the main reaction.

Of further reports we may mention that Bowden and Adkins[97] have reduced the optically active 2-phenyl-1-butanol and the active 3-phenyl-1-butanol to cyclohexylbutanols (68 and 91%, respectively, at 200°C. and 200 to 275 atmospheres); they believe that they have shown that no racemization occurs. At 220°C. 3-phenylpropanol[91] gives an 86% yield of cyclohexylpropanol and at 240°C. 3-(*o*-hydroxyphenyl)propanol gives approximately equal amounts of the cyclohexyl derivative and hexahydrochroman. Coumarin is reduced in two stages. In the first stage the double bond of the lactone ring is reduced (100°C., 90%) and in the second stage the benzene ring is reduced to octahydrocoumarin at 200° to 250°C. The second stage does not proceed smoothly, because a reduction of the carboxyl group to methyl occurs at the same time. Rather large amounts of polymers are formed as by-products at these high temperatures.

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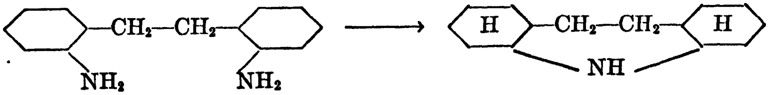
[95] Zartman, Cramer, and Adkins, *J. Am. Chem. Soc.*, **53**, 1425 (1931).

[96] Van Duzee and Adkins, *J. Am. Chem. Soc.*, **57**, 147 (1935).

[97] Bowden and Adkins, *J. Am. Chem. Soc.*, **56**, 689 (1934).

Durland and Adkins[98] reduced the nucleus of 2,2'-diaminodibenzyl and observed a ring closure at the same time.



In the case of naphthols, results different from previous ones have been obtained with Raney nickel. Palfray[99] and Musser and Adkins[100] worked upon this problem almost simultaneously. Naphthalene itself began to be reduced to tetralin at 100°C. and 150 atmospheres. According to Palfray, the further reduction of decalin started only at 170°C., according to Musser and Adkins, further reduction started slightly above 100°C. Thus they decided that Raney nickel was not very suitable for the production of tetralin. Palfray determined the best conditions for the reduction of naphthols. He found that the addition of hydrogen to naphthols started at 45° or 65°C. This meant that reduction started even in the solid phase, because he worked without solvents.

Alicyclic derivatives exclusively result from both naphthols. In the case of β-naphthol the yield is quantitative; in the case of α-naphthol 33% is split to tetralin. The formation of alicyclic tetralols is surprising, because mixtures of the alicyclic and aromatic tetralols are obtained with other nickel catalysts. In these mixtures the alicyclic portion predominates, Brochet and Cornubert, for example, reporting 85% alicyclic derivatives and 15% aromatic derivatives at 130° to 150°C. On the other hand, Musser and Adkins obtained the aromatic tetralol and its ethers by reducing α-naphthol and its esters at 150°C. (The reduction was said to start only at this temperature.) Cleavage and decalol formation occurred because of the high temperature. Naphthol and its ethers were reduced to aliphatic derivatives. The formation of an alicyclic ether exclusively is unusual, because blocking the hydroxyl group in the naphthols by means of ether or ester formation favors the reduction of the non-substituted nucleus. According to Palfray tetralol is reduced further to decalol at 120° to 125°C. The yields of β-decalol are good but those of α-decalol are only 53% because of cleavage of the OH group.

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[98] Durland and Adkins, *J. Am. Chem. Soc.*, **60**, 1501 (1938).
[99] Palfray, *Compt. rend.*, **206**, 1976 (1938).
[100] Musser and Adkins, *J. Am. Chem. Soc.*, **60**, 664 (1938).

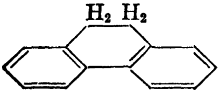
In the case of β-ethyl-α-naphthol and α-ethyl-β-naphthol the first addition of hydrogen occurs in the substituted nucleus.

Musser and Adkins describe the hydroxydiphenylenes and their ethers as similar to the naphthols. 2- and 3-hydroxybiphenyl are reduced to phenylcyclohexanols; 4-hydroxybiphenyl, on the other hand, gives a mixture of phenylcyclohexanol and cyclohexylphenol. The tendency for reduction of the non-substituted ring is increased with the ethers. The size of the alkyl group does not exert any particular influence in the case of the ethers, but even here the picture is not a clear one because of perhydrogenation and cleavage of the hydroxyl or ether group.

The reduction of phenanthrene is an example of the involved course which the reduction of multinuclear aromatic hydrocarbons can take. This reduction has been studied by Durland and Adkins.[101]

Carefully purified phenanthrene takes up 1 mole of hydrogen at 96°C., giving 9,10-dihydrophenanthrene (V). A copper-chromite catalyst is preferable for the production of this compound, because the temperature effect for further hydrogenation is greater with this catalyst than with Raney nickel. Raney nickel induces reduction of the hydrocarbon slightly above 100°C. all the way to symmetrical octahydrophenanthrene (VI). A mixture of VI and the asymmetric derivative VII occurs at 130°C. (67 or 29%). The intermediate product, tetrahydrophenanthrene (VIII) is obtained by the partial addition of 2 moles of hydrogen. In this case the dilution of hydrogen by nitrogen, which has been mentioned earlier, is recommended.

At 200°C. the addition of hydrogen gives dodecahydrophenanthrene (IX). The course of the reduction shows that the formation of this compound is related to a shift of the hydrogen atom during the intermediate stages. So it is not surprising that the individual intermediate compounds are disproportionated in the presence of nickel; for example, compound V is disproportionated to VIII and phenanthrene. Even on distillation this rearrangement occurs; for example, IX is changed to the isomer X.



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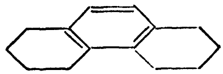

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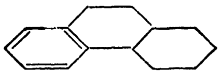

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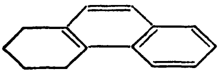

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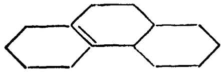

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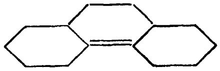

(X)

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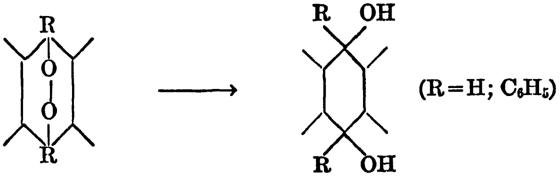
[101] Durland and Adkins, *J. Am. Chem. Soc.*, 59, 135 (1937); 60, 1501 (1938).

Dufraisse and Houpillart[102] have described the reduction of the "photooxides" of naphthacene, tetraphenylnaphthacene, anthracene, and mesodiphenylanthracene to the corresponding dihydroxy compounds. They reduced anthraquinone in the hope of obtaining a mesodihydroanthraquinone, too. They used the reduction method of Delépine and Horeau (presence of alkali) and obtained tetrahydroanthraquinone by way of the tetrahydroanthrahydroquinone. This reduction took place, like the reduction of anthraquinone, in the presence of platinum.[103]



12. Reduction of Heterocyclic Compounds

Reduction of furfural, the most important member of the furan series has often been the object of academic studies. Now that furfural is a large item of commercial production it is also the object of many technical investigations. The reduction requires mild conditions. Otherwise, the yields of furfuryl alcohol and tetrahydrofurfuryl alcohol are influenced strongly by the formation of condensation products, or of glycols caused by cleavage of the furan ring.

By the exercise of care, furfural can be reduced to furfuryl alcohol in the presence of Raney nickel. The temperature required for reduction of the nucleus is only slightly above that for reduction of the CO— group. For this reason Hilly[104] prefers to use copper-chromite. Furfural can be reduced to tetrahydrofurfuryl alcohol at 90°C. and 100 atmospheres. A 71% yield is obtained from pure starting material. With furfuryl alcohol as the starting material, 84% of tetrahydrofurfuryl alcohol is obtained at 50°C., this same yield being obtained at 125°C. with nickel on kieselguhr.

The nucleus of alkylfurans and alkenylfurans[105] can be reduced at 90° to 110°C. and 25 atmospheres; the unsaturated side chains absorb hydrogen even at room temperature. The yields are between 68%, with butyltetrahydrofuran, and 91% with the benzyl compound.

Paul[106] describes the reduction of a few furylalkylcarbinols in yields of 88 to 90% at 55° to 100°C. and initial pressures at approximately 90 atmospheres.

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[102] Dufraisse and Houpillart, *Compt. rend.*, 205, 740 (1937).
[103] Skita, *Ber.*, 58, 2685 (1925).
[104] Hilly, *Bull. soc. chim.*, 4, 1630 (1937).
[105] Paul, *Bull. soc. chim.*, 5, 1053 (1938).
[106] Paul, *Bull. soc. chim.*, 4, 846 (1937).

Raney nickel has also proved to be an outstanding catalyst for the reduction of carboxylic acids[107] such as pyromucic acid, furfuracrylic acid, furylidenemalonic acid, and others derived from furan. The furan nucleus is reduced without side reactions at 80° to 100°C. if the acids are reduced in the form of their salts, esters, or amides. Only with furfuracrylic acid has a slight cleavage been observed with the formation of propylbutyrolactone.

Furfural can be amidated at 50° to 200°C. and 50 to 120 atmospheres according to the U. S. Patent 2,109,159. There is formed about 45% furylmethylamine, about 6% secondary base, resins, and small amounts of tetrahydrofurylmethylamine.

Pyran, the higher ring homologue of furan does not appear to undergo side reactions, particularly hydrogen cleavages. Hydroxytetrahydropyran is obtained easily and in good yield by the Raney nickel reduction of pyrone; this reduction is said to proceed slowly and incompletely with platinum black and nickel catalysts. According to Blanchard and Paul[108] the reaction goes in two distinct steps. However, they have not undertaken any experiments to isolate tetrahydropyrone. A mixture of chromanones and hydroxychromans is obtained by the reduction of benzopyrones,[109] the chromones. Ethylchroman, for example, is converted at 100°C. into a mixture of 2-ethylchromanone and 2-ethyl-4-hydroxychroman, as much as 70% of the latter being formed.

Ethylchromone, which is reduced quantitatively to hexahydroethylchroman in the presence of Raney nickel, gives ethylchroman over copper chromite. 2-Phenylchromone, or flavone, is reduced incompletely at 85°C., 4-hydroxyflavone and starting material being obtained.

Raney nickel reduction of pyrrole and pyridine, the simplest of the heterocyclic compounds containing nitrogen, appears to have been studied only by Adkins and co-workers up to now.[110] Pyrrole and its alkyl derivatives, in so far as the nitrogen is free from substituents, can be reduced only with difficulty. Absorption of hydrogen stops prematurely and cannot be started by the introduction of fresh catalyst. If an attempt is made to force the reduction, the yield of pyrrolidine derivatives remains unchanged, the non-reduced portion being transformed to high boiling compounds. At 180°C. and approximately 200 atmospheres pyrrole gives 47% of pyrrolidine and 48% of unchanged compound. In the case of 2,4-diethyl-3,5-dimethylpyrrole a 70% yield of the corresponding tetraalkylpyrrolidine can be obtained.

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[107] Paul and Hilly, *Compt. rend.*, **208**, 359 (1939).

[108] Blanchard and Paul, *Compt. rend.*, **200**, 1414 (1935).

[109] Mozingo and Adkins, *J. Am. Chem. Soc.*, **60**, 669 (1938).

[110] Adkins and Signaigo, *J. Am. Chem. Soc.*, **58**, 709 (1936). Adkins, Kuick, Farlow, and Wojcik, *J. Am. Chem. Soc.*, **56**, 2425 (1934).

The presence of a carbalkoxy substituent on the pyrrole nucleus stops hydrogenation completely. The nucleus can be reduced over copper chromite only under drastic conditions after the carbalkoxy group has either been reduced to the methyl group or has been completely split off. Under these conditions an alkylation of the nitrogen occurs at the same time, the yield being poor. For example, carbethoxypyrrole at 250°C. over Raney nickel gives 10% of 1-ethylpyrrolidine as a result of decarboxylation and alkylation. When 2-carbethoxy-4-ethyl-3,5-dimethylpyrrole is reduced at this same temperature, there is formed simultaneously 1,3-diethyl-2,4,5-trimethylpyrrolidine as a result of the reduction of the ester group, and 1,3-diethyl-4,5-dimethylpyrrolidine as a result of decarboxylation, a total yield of approximately 37% being obtained.

Adkins and Coonradt[111] reported both the complete and selective hydrogenation of several phenylpyrroles, indoles, carbazoles, and acridines over copper chromite and Raney nickel. All these compounds were completely hydrogenated best over Raney nickel, 80% yields being obtained.

In general, although results were similar, copper chromite catalyst was preferred for selective reduction. The pyrroloid ring of the indoles and phenylpyrroles was hydrogenated readily. The carbazoles were much more resistant to catalytic hydrogenation but tetra-, hexa-, and dodecahydrocarbazoles were obtained in yields of 72, 16, and 85%, respectively.

Acridine proved to be extremely reactive toward hydrogen. 1 mole of hydrogen was absorbed at room temperature over Raney nickel with the formation of 9,10-dihydroacridine. More vigorous conditions (30 minutes at 100°C.) resulted in a mixture of octa- and dodecahydroacridines. The complete hydrogenation to tetradecahydroacridine was effected successfully over nickel at 240°C.

As a result of the reactivity of pyrrolcarboxylic esters, acetyl and aldehyde groups which are within these compounds can be reduced to ethyl and methyl groups. A 95% yield of 2-carbethoxy-4-ethyl-3,5-dimethylpyrrole is obtained at 170°C. from 2-carbethoxy-4-acetyl-3,5-dimethylpyrrole and a 90% yield of 2,3,4-trimethyl-5-carbethoxypyrrole is obtained at 150° to 160°C. from 2,4-dimethyl-5-carbethoxypyrrole-3-aldehyde.[112] 4-Methyl-2-ethyl-5-carbethoxypyrrole-3-aldehyde behaves similarly. Greater or lesser amounts of the corresponding pyromethane result if the aldehyde is not pure. Temperatures above 170°C. are to be avoided during reduction of pyrrole derivatives if alcohols are used as solvents. Above this temperature alkylation of the nitrogen results. The reduction of 2,4-diacetyl-3,5-dimethylpyrrole in alcohol at 200°C. gives 1,2,4-triethyl-3,5-dimethylpyrrolidine.

[111] Adkins and Coonradt, *J. Am. Chem. Soc.*, **63**, 1563 (1941).

[112] Fischer and Hofelmann, *Ann.*, **533**, 216 (1938).

If the pyrrole nucleus has a substituent on the nitrogen, this class of compounds is reduced rather easily. At 135°C. 1-phenylpyrrole gives a mixture of 63% phenylpyrrolidine and 30% of cyclohexylpyrrolidine. The pyrrole nucleus is reduced more readily than that of benzene. Both nuclei are reduced to completion at 180°C., an 84% yield of cyclohexylpyrrolidine resulting. 1-Carbethoxypyrrole can be reduced at 160°C. to the corresponding pyrrolidine; 1,2-dicarbethoxypyrrole starts to absorb hydrogen even at room temperature and can be reduced at 50°C. in almost quantitative yield.

Whereas the reduction of pyrroles never becomes easier as a result of the presence of substituents in the nucleus, but instead, always seems to become more difficult, the opposite appears to be true with pyridines. The presence of substituents like alkyl, phenyl, acetyl, or carbalkoxy improves the reduction so that pyridine itself requires the most drastic conditions or the highest temperature. It is converted to a 83% yield of piperidine at 200°C. Picoline still requires the same temperature. A temperature of 175°C. is required with the followng compounds: 2,6-dimethylpyridine (92%), 4-phenylpyridine (85%), 2,6-diphenylpyridine (66%), and 2,6-di-(*β*-phenylethyl)pyridine.

In the case of 2-(phenylalkyl) derivatives the temperature required for reduction decreases with diminishing length of the side chain: 160°C. for *δ*-phenylbutyl- and *γ*-phenylpropylpyridine (81%, 89%), 125°C. for *β*-phenylethylpyridine (95%), and 100°C. for 2-benzylpyridine (6%). The benzene nucleus of the compounds mentioned is not reduced under these conditions. Nicotinic acid esters are reduced at 165°C. in 80% yields, if alcohols are avoided as solvents. Like pyrrole they produce *N*-alkyl derivatives at the high temperatures. The reduction of quinolinic acid esters is especially difficult, because condensation products which may be formed readily at the high temperatures can act as poisons on the catalyst. However, this compound can be reduced at 125°C. in dioxane, as much as a 77% yield of piperidine-2,3-dicarboxy ester being obtained. No simple reduction can be carried out with 3-acetylpyridine. There is obtained 3-ethylpiperidine and 3-methylpiperidylcarbinol, of which 61% is isolated under particularly favorable circumstances.

Raney nickel has proved to be superior to nickel on kieselguhr for these reductions which are carried out between 150 and 300 atmospheres, because Raney nickel permits either the use of lower temperatures or more rapid completion of the hydrogenation.

Reduction of 1,3-diketones derived from nicotinic acid results in reduction of the pyridine nucleus, but mainly in cleavages at both carbonyl groups.[113]

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[113] Adkins and Kuick, *J. Am. Chem. Soc.*, 57, 143 (1935).

Quinoline is reduced at 200°C. to a 95% yield of a mixture of *cis-* and *trans*-decahydroquinoline. Escourrou[50] reduced 6-methylquinoline under reduced pressure and obtained tetrahydromethylquinoline, as well as the decahydro compound.

Of other heterocyclic rings only the benzyl derivative of hydrouracil[114] and a few pyrazolones appear to have been studied with Raney nickel.[115] First of all, 6-benzyluracil gives 6-benzylhydrouracil (53%) at 175°C.; from this compound is obtained 2-keto-6-hexahydrobenzylhexahydropyrimidine (26%) at 225°C. With 5-benzyluracil there is formed 5-hexahydrobenzylhydrouracil (59%) in the first step of reduction, and the corresponding pyrimidine (42%) in the second step. In both cases an acid amide group is reduced during the second step.

Pyrazolones behave like the open compounds containing a singly or doubly bound nitrogen bridge (aldazines, hydrazones, and azo compounds); they are split open at the nitrogen bridge. As a result β-amino acids must be formed. However, in these compounds the amino group is held rather loosely; it is eliminated with the formation of carboxylic acid amides. A 68% yield of butyranilide is formed at 150°C. from 1-phenyl-3-methylpyrazolone and a 95% yield of hydrocinnamanilide is formed from 1,3-diphenylpyrazolone. If the 4 position of the pyrazolone is occupied by an alkyl or alkal group, the amino group is not removed during the reduction. For example, 1-phenyl-3-methylbenzalpyrazolone gives an 80% yield of 2-amino-1-benzylbutyranilide.

To conclude this discussion of reduction of heterocyclic ring systems we shall mention briefly the formation of nitrogen heterocycles by the hydrogenation of certain compounds. The formation of pyrrolidone during the reduction of nitrile esters and of oxime esters has already been mentioned. The formation of pyrazines during the reduction of α-diketone monoximes and dioximes is not entirely clear.[116] In a few instances, small portions of diamines or amino alcohols result during the hydrogenation of these compounds. The chief products are the pyrazines. For example, 18% of 2,3-diaminobutane and 76% of tetramethylpyrazine hydrate are obtained from dimethylglyoxime, and 36% of 1,2-diphenylethanolamine and 42% of tetraphenylpyrazine from benzil monoxime. Pyrazines are obtained exclusively from other oximes, examples being 2,5-dimethyl-3,6-dicarbethoxypyrazine from nitrosoacetoacetic ester, 2,5-diphenylpyrazine from nitrosoacetophenone, and 2,3,5,6-diindenopyrazine from nitrosohydrindone. These reactions are carried out at 70° to 100°C. and 100 to 150 atmospheres.

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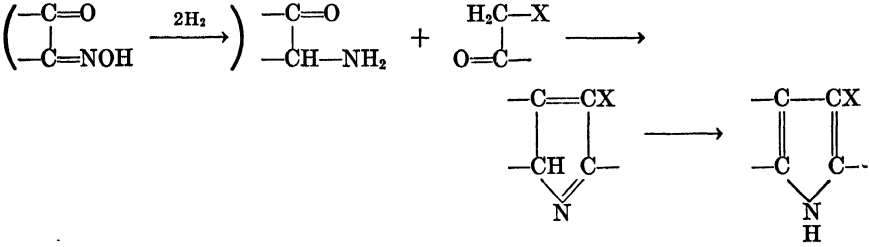
[114] Ambelang and Johnson, *J. Am. Chem. Soc.*, 61, 74 (1939).

[115] Adkins and Winans, *J. Am. Chem. Soc.*, 55, 4167 (1933).

[116] Adkins and Winans, *J. Am. Chem. Soc.*, 55, 2051 (1933).

Off-hand the formation of piperazine might be expected. The oximino group reacts at appreciably greater speed than the keto group with hydrogen. An amino ketone would be expected as an intermediate and 2 molecules of this intermediate would combine like those amidations of carbonyl compounds according to Mignonac's method, a piperazine ring being formed.

Adkins and Winans[115] have carried out the well known Knorr pyrrole synthesis catalytically with Raney nickel. An example of the Knorr synthesis is given by 2,4-dimethylpyrrole-3,5-dicarboxylic ester formed by the reduction of a molecular mixture of nitrosoacetoacetic ester and acetoacetic ester with zinc dust and acetic acid. A pyrrole ring is formed according to the following scheme:



(X = —COR, —CN, —COOR)

The hydrogenations were carried out at 70° to 90°C. by use of the following components: I, acetylacetone; II, acetoacetic ester; III, nitrosoacetoacetic ester; and IV, nitrosoacetylacetone. The following compounds were obtained: with I and III, 63% of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole; with II and III, 67% of 2,4-dimethyl-3,5-dicarbethoxypyrrole; with II and IV, 74% of 2,4-dimethyl-5-acetyl-3-carbethoxypyrrole; and with I and IV, 55% of 2,4-diacetyl-3,5-dimethylpyrrole.

Hydrogenation with Copper Chromite Catalysts

BY CH. GRUNDMANN

Translated by DONALD M. BURNESS

I. INTRODUCTION

Since the discovery by Sabatier in 1897 of a method for the catalytic combination of hydrogen with organic compounds, numerous methods have been developed for carrying out this reaction which is of such great importance to the organic chemist. Of the many catalysts which have been proposed for catalytic hydrogenations four are considered to be of especial value in the laboratory; namely, platinum, palladium, nickel, and copper chromite. The noble metal catalysts, because of their high cost and the unusually mild conditions under which they are active, are used almost exclusively for special purposes, such as analytical determinations and the hydrogenation of small amounts of precious substances. The base metal catalysts, on the other hand, although requiring higher temperatures and pressures, gradually have come into great prominence in the field of organic synthesis. This has been especially true of the various nickel catalysts, notably Raney nickel.[1]

In recent years another type of catalyst, copper chromite, has been developed. These new copper chromite catalysts supplement the nickel catalysts in many respects and provide the organic chemist with another useful tool. Credit for the introduction of this new method of hydrogenation into organic laboratory practice belongs to Adkins[2] and his associates, who since 1931 have carried out an extensive series of investigations in this field. However, even before the appearance of the first American work in this field, the German chemical industry, as a result of its experience with methanol synthesis, had developed catalysts which closely resembled those of Adkins in principle. With these catalysts it was possible to carry out the same reductions for which copper chromite has proved especially suitable; for example, the preparation of alcohols from carboxylic esters.[3]

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[1] See chapter by Schröter, "Hydrogenation with Raney Nickel Catalysts," p. 61.

[2] Adkins, *Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts*, University of Wisconsin Press, Madison, 1937.

[3] German Patents, 573,604 (1925), 629,244 (1928), 607,792 (1928).

The appearance of the first work of Adkins[4] induced various industrial laboratories to publish their results in scientific periodicals.[5]

II. PROPERTIES AND EXPERIMENTAL CONDITIONS FOR USE OF COPPER CHROMITE CATALYSTS

Copper chromite is especially active toward those functional groups which contain oxygen, whereas the nickel catalysts generally are more suitable for the hydrogenation of carbon to carbon multiple bonds. In the hydrogenation of an unsaturated ketone, for example, the carbonyl group is reduced preferentially when copper chromite is used as the catalyst, while in the presence of nickel the double bond is attacked first. Likewise, most aryl groups are stable in the presence of copper chromite, even under the drastic conditions used for the reduction of amides and esters. Thus, it is apparent that the nickel and copper chromite catalysts supplement each other in a manner most fortunate for the ready solution of many problems in organic synthesis.

Unlike the nickel catalysts, copper chromite belongs to the group of oxide catalysts in which the essential active state is not a finely divided metal, but a metal oxide which is not reduced to the free metal during the hydrogenation process. In the present case the real catalyst is probably copper oxide, which is stabilized against reduction by chromium oxide. Addition of the oxide of an alkaline earth metal also aids in the stabilization[6] (see Section III). In any event, conversion of the black cupric oxide to the red and relatively inactive cuprous compound must be avoided.

It has already been intimated that hydrogenation with copper chromite catalysts requires elevated temperatures and pressures. At low pressures the catalyst is useless, presumably because insufficient hydrogen is adsorbed at its active centers.

PRESSURES which can be used are necessarily limited by the equipment available for the compression of hydrogen and by the strength of the bomb. Hydrogen is available in commercial cylinders at a pressure of 125 atmospheres, which is adequate for most purposes. Thus, a bomb of ordinary laboratory size can be filled with hydrogen to 100 atmospheres pressure which will rise to 175 atmospheres at 250°C. In general, a hydrogen pressure (compressed cold) of 40 to 200 atmospheres is used.

It should be pointed out that in many instances an increase in the pressure of hydrogen greatly accelerates the rate of hydrogenation. Folkers and Adkins[7] observed the following influence of pressure of hydrogen on the rate of hydrogenation of ethyl laurate. When 30 g. of the ester were hydrogenated at 250°C. in the presence of 3 g. of copper chromite, the reduction was complete in 7 hours at 106 atmospheres, in 1 hour at 214 atmospheres, and in 15 minutes at 333 atmospheres. Thus, by a 2-fold increase in pressure a 7-fold increase in rate was accomplished, while a 3-fold increase in pressure caused a 28-fold increase in the rate of hydrogenation. Similarly, in the hydrogenation of 100 g. of acetone to isopropyl alcohol with 1 g. of copper chromite for 30 minutes the hydrogenation was 17% complete at 35 atmospheres, 60% complete at 148 atmospheres, and 95% complete at 212 atmospheres. After 1 hour the reaction had proceeded to the extent of 22, 92, and 100%, respectively, at the three different pressures.

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[4] Adkins and Connor, *J. Am. Chem. Soc.*, **53**, 1091 (1931).

[5] Schrauth, Schenck, and Stickdorn, *Ber.*, **64**, 1314 (1931); Normann, *Angew. Chem.*, **44**, 714 (1931); Schmidt, *Ber.*, **64**, 2051 (1931).

[6] Connor, Folkers, and Adkins, *J. Am. Chem. Soc.*, **53**, 2012 (1931).

[7] Folkers and Adkins, *J. Am. Chem. Soc.*, **54**, 1145 (1932).

The hydrogenation of ethyl pivalate, ethyl β,β-dimethylglutarate, ethyl succinate, and ethyl camphorate gave poor yields of the corresponding alcohols at pressures below 200 atmospheres.

In many cases the unfavorable influence of low pressure can be counteracted by the use of more catalyst or a higher temperature. However, a modern, well equipped laboratory should be provided with an apparatus for the compression of hydrogen, especially since such equipment can be purchased at moderate cost.

TEMPERATURES at which hydrogenations with copper chromite proceed at reasonable rates always lie above 100°C. To specify an upper limit is difficult, but in general there is nothing to be gained by exceeding 280°C.

ACTIVITY of the copper chromite catalysts is of the same order of magnitude as that of platinum, palladium, and nickel catalysts. Adkins[2] gives the following approximate values for the ratio of catalyst to hydrogen acceptor for the reduction of 50 to 100 g. of compound under laboratory conditions (the percentages representing the weight of catalyst in terms of the weight of hydrogen acceptor): Aldehydes and ketones require 2 to 4% of the catalyst; simple esters, 3 to 5%; malonates, succinates, etc., 5 to 10%; amides, 10 to 15%. For other types of reduction the use of 5 to 10% of the catalyst is suggested.

If, as is often the case, the correct ratio must first be determined, this summary furnishes a satisfactory approximation for the initial experiment. However, it should be emphasized that the rate of hydrogenation at constant ratio of catalyst to hydrogen acceptor is by no means independent of the size of the batch. No exact figures are available, but, if 2.5 g. of catalyst are required for 50 g. of compound, it is likely that 10 to 12 g. of catalyst will be entirely adequate for 500 g. of the same material.

The copper chromite catalysts appear to be rather immune to poisoning; at least they are immune to a much greater degree than are the noble metal and nickel catalysts. However, the hydrogenation may be retarded or completely halted by the presence of organic halogen or sulfur compounds in the material to be hydrogenated. It is futile in this case to attempt to induce hydrogenation by an increase in temperature or pressure, but the effect of the impurities can be reduced many-fold, or completely eliminated, by use of a greater amount of catalyst. In fact, an excellent method for the removal of all traces of halogen and sulfur from a compound to be hydrogenated is by treatment of the compound with 5 to 10% of its weight of copper chromite under hydrogen at 100°C.

Solvents are not always necessary and their use is often undesirable. However, they may be used to advantage in the hydrogenation of solid, high melting materials, and also when undesirable side reactions must be avoided. They also are useful for a better dispersion of the catalyst and whenever the separation of two immiscible liquids must be prevented. The solvents recommended by Adkins for hydrogenations with copper chromite are ethyl alcohol, dioxane, ether, and methylcyclohexane.

Ethanol is an excellent solvent for a large variety of compounds, especially at temperatures of 100° to 200°C. Although its critical temperature is 242°C., its use above 200°C. is not practical owing to inaccuracies introduced in the measurement of the hydrogen pressure. Ethanol is completely stable toward copper chromite and hydrogen up to at least 270°C. Because of its miscibility with water, which is often formed during the hydrogenation, formation of separate phases is avoided.

In spite of these advantages ethanol is not always a suitable solvent; thus, it cannot be used in the hydrogenation of amides, since they readily undergo alcoholysis at 150° to 200°C.

$$\mathrm{RCONH_2 + C_2H_5OH \longrightarrow RCO_2C_2H_5 + NH_3}$$

Also, in the reduction of esters transesterification might occur and cause difficulty in the subsequent separation of the various fractions of the product. 1,3-Diketones may also undergo alcoholysis at 150° to 250°C.

$$\mathrm{RCOCH_2COR + C_2H_5OH \longrightarrow RCO_2C_2H_5 + CH_3COR}$$

β-Keto esters, on the other hand, are stable under these conditions. Finally, ethanol cannot be used when the reaction mixture contains a primary or secondary amine, since alkylation might occur.

Dioxane is one of the most useful solvents for hydrogenation with copper chromite. It can be used at temperatures up to 275°C., it is an excellent solvent for a large number of substances, and it is miscible with water. Many hydrogenations proceed more rapidly in dioxane than in any other solvent. The chief disadvantage of dioxane lies in the difficulty of isolation of reaction products which boil below 150°C.

Ether is a useful solvent, but it has the disadvantage of a low critical temperature (192°C.), making its use impractical at temperatures above 175°C.

Methylcyclohexane remains liquid and is absolutely stable under the most drastic conditions of hydrogenation. These properties make it a valuable solvent. The disadvantages of methylcyclohexane are its limited solvent power and its immiscibility with water, which might lead to lumping and inactivation of the catalyst by water formed in the reduction.

III. PREPARATION OF CATALYST[8]

According to Adkins a suitable catalyst can be prepared by any method which produces copper oxide in combination with a stabilizing substance such as chromium oxide. Even the pure, intimate, mechanical mixture of copper oxide and chromium oxide, or the thermal treatment of such a mixture, furnishes a satisfactory catalyst.[2,9] The best laboratory method for preparation of the catalyst for use in a rocking bomb is the thermal decomposition of copper ammonium chromate. The product so obtained is very finely divided and is readily suspended in the reaction mixture. The addition of a barium, calcium, or magnesium compound was observed by Adkins and collaborators[6,9] to stabilize the catalyst further against reduction to the red inactive form. Two reliable methods for the preparation of copper chromite catalysts are given below.

COPPER CHROMITE, ACCORDING TO ADKINS.[2,4,10] 900 ml. of a solution of 260 g. of copper nitrate trihydrate and 31 g. of barium nitrate are heated to 80°C. and poured into 900 ml. of a solution at 25°C. which contains 151 g. of ammonium dichromate and 225 ml. of 28% ammonium hydroxide. The precipitate formed is filtered, and the cake pressed with a spatula and sucked as dry as possible. The product is dried for 12 hours in an oven at 75° to 80°C. and pulverized. The thermal decomposition is carried out in three portions in a large porcelain dish (15 cm. in diameter) by heating over a free flame. The powder is stirred constantly with a spatula during the decomposition, and the flame is so adjusted that the evolution of gas is not too violent. The decomposition should take place at the lowest possible temperature. This is best accomplished by heating only one side of the dish and increasing the rate of stirring as soon as decomposition sets in, so that it is spread throughout the entire mass. The color of the powder gradually changes from orange to brown and finally to black. When the mass has become uniformly black and the evolution of gas has subsided, the powder is allowed to cool. The three portions are combined and stirred for 30 minutes with 600 ml. of 10% acetic acid. The product is filtered, washed with six 100 ml. portions of water, dried for 12 hours at 125°C., and pulverized. The yield of catalyst is 170 g.

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[8] See also U. S. Patents 2,089,433 [*Chem. Abstracts*, 31, 7066 (1937)], 2,129,507 [*Chem. Abstracts*, 32, 8716 (1938)].

[9] Connor, Folkers, and Adkins, *J. Am. Chem. Soc.*, 54, 1138 (1932).

[10] See also Blatt, ed., *Organic Syntheses*, Wiley, New York, 1943, Coll. Vol. II, p. 144, note 11.

Copper Chromite, According to Lazier and Arnold.[11] A mixture of 26 g. (0.1 mole) of c.p. barium nitrate and 800 ml. of distilled water is heated to 70°C. When solution is complete, 218 g. (0.9 mole) of c.p. copper nitrate trihydrate are added and the mixture stirred at 70°C. until a clear solution is attained. Barium nitrate is not very soluble in cold water and still less so in copper nitrate solution; therefore, it is necessary to make up the solution in the correct sequence and by heating.

A solution of ammonium chromate is prepared by dissolving 126 g. (0.5 mole) of c.p. ammonium dichromate in 600 ml. of distilled water and adding 150 ml. of 28% aqueous ammonia (sp. gr. 0.9). The warm, freshly prepared solution of ammonium chromate may be used immediately or first cooled to room temperature. However, since it is supersaturated, crystals separate upon long standing in the cold. The ammonium chromate solution is poured in a fine stream into the warm solution of the nitrate while being stirred by hand. Stirring is continued for a few minutes and then the reddish brown precipitate of copper barium ammonium chromate is collected and pressed on a 16 cm. suction filter, and dried at 100°C. The dry precipitate is placed in a covered nickel dish (about 6 cm. deep, 19 cm. long, and 10 cm. wide), or in one or two small porcelain dishes covered with watch-glasses, and heated in a muffle furnace for 1 hour at 350° to 450°C. The decomposition of the copper ammonium chromate is an exothermic reaction, and is accompanied by a vigorous evolution of gas; therefore, in order to avoid considerable mechanical loss, the dishes should not be too full. It is also inadvisable to pulverize the dried precipitate, since the coarse, lumpy structure helps prevent the material from flying apart. When the decomposition is complete, the product, which should consist of about 160 g. of a bluish black, brittle powder, is ground in a mortar until all hard lumps are pulverized. This crude catalyst, which still contains excess copper oxide, is satisfactory for the dehydrogenation of alcohols and for the less difficult hydrogenations, such as the reduction of nitro groups. A more active catalyst is obtained by removal of the copper oxide by an acid extraction. The powder is treated in a 2 liter beaker with 1200 ml. of 10% acetic acid. After being stirred for 10 minutes, the mixture is allowed to stand, and two-thirds or more of the acid solution is decanted and replaced by 1200 ml. of fresh 10% acetic acid. The extraction is repeated once more and the residue washed by decantation with four 1200 ml. portions of distilled water. Prolonged washing is inadvisable, since the catalyst tends to become colloidal. Finally it is filtered by suction, dried at 110°C., and pulverized once again. The finished product is a fine black powder weighing 130 to 140 g., and is entirely unaffected by exposure to air and moisture. The addition of barium nitrate to the mixture can be omitted, although it is said to increase the resistance of the catalyst toward reduction and sulfur poisoning. If the barium salt is omitted, 242 g. of copper nitrate trihydrate are used; otherwise, the procedure is as described above.

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[11] Blatt, ed., *Organic Syntheses*, Wiley, New York, 1943, Coll. Vol. II, p. 142. See also U. S. Patents 1,746,782, 1,146,783, and 1,964,000.

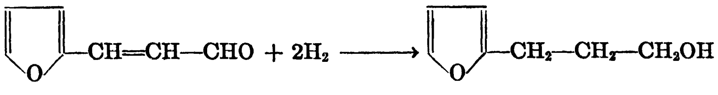
IV. HYDROGENATION OF FUNCTIONAL GROUPS

1. Reduction of Carbon-Carbon Double Bond, and of Aromatic and Heterocyclic Nuclei

It has already been stated that copper chromite is less suitable than nickel catalysts for the reduction of the alkene linkage because of the high temperatures required (100° to 175°C.). Nevertheless, there are occasions when it may be used to advantage for this purpose. For example, if the molecule contains a carbonyl or carbalkoxy group which must also be reduced, both reactions can be carried out conveniently and simultaneously with copper chromite as catalyst. Thus, ethyl cinnamate (70 g.) was reduced to 3-phenyl-1-propanol in 83% yield in the presence of 6 g. of copper chromite. The reaction was carried out at 250°C. and 220 atmospheres and was complete in 3 hours.[12]

$$C_6H_5—CH{=}CH—COOC_2H_5 + 3H_2 \longrightarrow C_6H_5—CH_2—CH_2—CH_2OH + C_2H_5OH$$

The use of copper chromite is also recommended when it is desirable to avoid the hydrogenation of a benzene or furan ring which is present in the compound. (See also Section V on selective hydrogenation.) The reduction of 90 g. of β-furylacrolein to 3-(2-furyl)-1-propanol in 72% yield was carried out in 96 minutes at 175°C. and 100 to 200 atmospheres with 15 g. of catalyst.[13]



Partial hydrogenation of an acetylenic compound to the corresponding ethylenic derivative has been observed in the case of 2-butyne-1,4-diol, which was reduced to 2-butene-1,4-diol.[14]

The benzene ring does not undergo hydrogenation with copper chromite except in special cases.[15] Phenanthrene, however, is reduced in 88% yield to 9,10-dihydrophenanthrene at 130°C. and 150 to 200 atmospheres;

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[12] Adkins and Folkers, *J. Am. Chem. Soc.*, **53**, 1095 (1931).

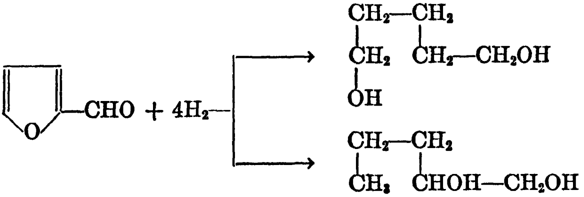
[13] Burdick and Adkins, *J. Am. Chem. Soc.*, **56**, 438 (1934).

[14] French Patent, 857,914 (*Chem. Zentr.*, **1941**, I, 2320).

[15] Connor and Adkins, *J. Am. Chem. Soc.*, **54**, 4678 (1932); Signaigo and Adkins *ibid.*, **58**, 709 (1936).

at 220°C. the hydrogenation proceeds further to give 1,2,3,4,5,6,7,8-octahydrophenanthrene.[16,17] In a similar manner anthracene is converted almost quantitatively to 9,10-dihydroanthracene.[16] Naphthalene can be hydrogenated at about 200°C., but only as far as tetralin.[18]

The furan ring resists hydrogenation at temperatures below 160°C.; at higher temperatures cleavage of the ring occurs. From furfural and furfuryl alcohol a mixture of 1,5-pentanediol and 1,2-pentanediol is obtained at temperatures above 170°C. Hydrogenation of 80 g. of furfuryl alcohol with 3 g. of catalyst was carried out at 175°C. and 100 to 150 atmospheres; after 11.5 hours a 70% yield of a mixture of 1,2-pentanediol and 1,5-pentanediol was obtained.



According to the meager data available, it appears that the pyridine ring is more readily hydrogenated than is the benzene nucleus. Pyridine, itself, with copper chromite at 220°C. and 100 to 150 atmospheres of hydrogen yields only 50% of the theoretical amount of piperidine.[4] The method, therefore, is of no value in this case, since considerably better yields are obtained with nickel catalysts. On the other hand, quinoline is converted in excellent yield (97%) to 1,2,3,4-tetrahydroquinoline at 190°C. and 100 to 150 atmospheres with 10% of its weight of catalyst.[4]

Of all the aromatic ring systems which have been investigated, the pyrrole nucleus is the most difficult to hydrogenate. With copper chromite at temperatures above 200°C. pyrrole is converted to pyrrolidine in 50% yield; similar results are obtained with substituted pyrroles.[19] Better yields are obtained in all cases with nickel catalysts at lower temperatures.

It might be appropriate to mention here that hydrogenation of methanol–lignin with copper chromite in dioxane at 260°C. and 220 atmospheres yielded, in addition to 28% of methanol, 44% of a mixture of 4-*n*-propylcyclohexanol, 4-*n*-propylcyclohexane-1,2-diol, and 3-(4-hydroxycyclohexyl)-1-propanol.[20] With soda–lignin other predominantly high molecular products were obtained.[21]

[16] Burger and Mosettig, *J. Am. Chem. Soc.*, **57**, 2731 (1935); **58**, 1857 (1936).

[17] Durland and Adkins, *J. Am. Chem. Soc.*, **59**, 135 (1937); **60**, 1501 (1938).

[18] Adkins and Reid, *J. Am. Chem. Soc.*, **63**, 741 (1941).

[19] Signaigo and Adkins, *J. Am. Chem. Soc.*, **58**, 709 (1936); Rainey and Adkins, *ibid.*, **61**, 1104 (1939).

[20] Harris, D'Ianni, and Adkins, *J. Am. Chem. Soc.*, **60**, 1467 (1938); see also U. S. Patent, 2,146,655.

[21] Adkins, Frank, and Bloom, *J. Am. Chem. Soc.*, **63**, 549 (1941).

2. Replacement of Alcoholic Hydroxyl, Carbonyl, and Carbalkoxy Groups by Hydrogen

The hydroxyl group in primary and secondary alcohols and in phenols is so resistant to reduction that the reaction:

$$ROH + H_2 \longrightarrow RH + H_2O$$

has not been observed at temperatures below 250°C. except in a few special cases; for example, when R contains a phenyl group in the vicinity of the hydroxyl group. Thus, benzyl alcohol is converted readily to toluene, and β-phenylethanol and 2-phenyl-1-butanol yield the corresponding hydrocarbons, ethylbenzene and 2-phenylbutane, at temperatures above 200°C.

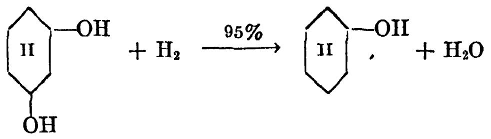
$$C_6H_5—CH_2—OH + H_2 \longrightarrow C_6H_5—CH_3 + H_2O$$

$$C_6H_5—CH_2—CH_2OH + H_2 \longrightarrow C_6H_5—CH_2—CH_3 + H_2O$$

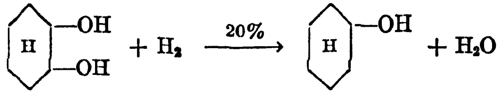
$$\underset{\textstyle C_2H_5}{C_6H_5—CH—CH_2OH} + H_2 \longrightarrow \underset{\textstyle C_2H_5}{C_6H_5—CH—CH_3} + H_2O$$

Similarly, the carbinol group is activated by the proximity of a furan or pyrrole ring. These reactions are often troublesome in the reduction of carboxylic esters to the primary alcohols (see page 114), since in the cases mentioned above the hydroxyl group is eliminated at temperatures equal to, or even lower than, those required for its formation from the acid radical.

In 1,2- and particularly in 1,3-glycols one of the two hydroxyl groups is replaced readily by hydrogen at temperatures above 200°C. This fact is well illustrated by the behavior of the three position isomers of cyclohexanediol toward copper chromite.[22] While the 1,4 isomer is absolutely stable, 95% of 1,3-cyclohexanediol is converted to cyclohexanol after 3 hours at 200°C.



1,2-Cyclohexanediol is somewhat more resistant to hydrogenation; at 250°C. only 20% is reduced to cyclohexanol after 6 hours.



1,3-Propanediol, after 72 minutes at 250°C., yields 94% of the theoretical amount of n-propanol. Likewise, glycerol is converted to propylene glycol in 85% yield, while from 1,3-butanediol a mixture of 56% of 2-butanol and 32% of 1-butanol is obtained.[13]

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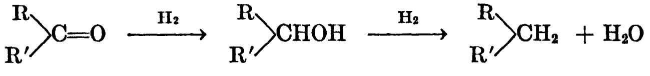
[22] Connor and Adkins, *J. Am. Chem. Soc.*, 54, 4678 (1932).

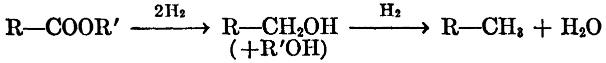
With the possible exception of the furan ring (see page 121), cleavage of ethers and acetals by hydrogen in the presence of copper chromite has not been observed.

In Section 3, below, it is shown that, in general, aldehydes and ketones are reduced with copper chromite to the corresponding primary or secondary alcohols under conditions considerably milder than those required for the replacement of the hydroxyl group by hydrogen. However, complete conversion of the carbonyl to the methylene group is often accomplished with relative ease. For example, benzophenone is converted



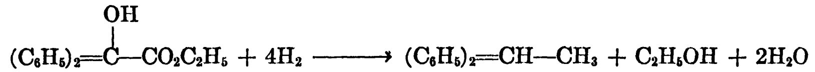
$$\begin{matrix}R\\R'\end{matrix}\!\!>C{=}O \xrightarrow{H_2} \begin{matrix}R\\R'\end{matrix}\!\!>CHOH \xrightarrow{H_2} \begin{matrix}R\\R'\end{matrix}\!\!>CH_2 + H_2O$$

to diphenylmethane in 97% yield at 175°C. and 100 to 150 atmospheres; likewise, an excellent yield of 1,2-diphenylethane is obtained from benzoin.[4] Hydrocarbons also may be formed from carboxylic esters in one operation,



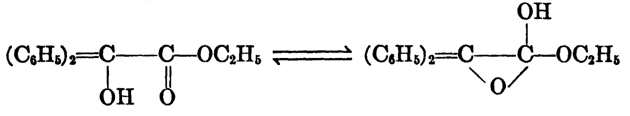
$$R{-}COOR' \xrightarrow{2H_2} \underset{(+R'OH)}{R{-}CH_2OH} \xrightarrow{H_2} R{-}CH_3 + H_2O$$

provided the necessary activating groups are present (see above). Thus, ethyl benzoate is converted quantitatively to toluene,[2] and diethyl phthalate yields *o*-xylene in 84% yield after 2 to 3 hours at 250°C. and 170 atmospheres with 25% by weight of catalyst.[23] Ethyl benzilate is reduced to 1,1-diphenylethane in 93% yield under such mild conditions (175°C.)



$$(C_6H_5)_2{=}\overset{OH}{\overset{|}{C}}{-}CO_2C_2H_5 + 4H_2 \longrightarrow (C_6H_5)_2{=}CH{-}CH_3 + C_2H_5OH + 2H_2O$$

that Adkins[2] was led to assume that the hydrogenation occurs on a tautomeric form of the ester, a hemiacetal of an oxido ketone.



Later it was discovered that the normal reaction product, 1,1-diphenyl-1,2-ethanediol can be obtained by use of a still lower temperature (125°C.) and dilution of the mixture with alcohol.[23]

3. Reduction of Aldehydes and Ketones to Alcohols

The carbonyl group in aldehydes and ketones is reduced readily to the hydroxyl group with copper chromite under fairly mild conditions, 125°

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[23] Adkins, Wojcik, and Covert, *J. Am. Chem. Soc.*, 55, 1669 (1933).

to 150°C. and 100 atmospheres pressure. The yields of the corresponding carbinols are in most instances nearly quantitative. For this type of reduction the copper chromite catalyst is unexcelled; the danger of encountering undesirable side reactions is considerably less than when a nickel catalyst is used. Aldo and keto alcohols and esters likewise are reduced with ease to the corresponding glycols or hydroxy esters. If an alkene linkage is present, it also will be reduced, for it is impossible to carry out a selective hydrogenation under the conditions necessary for the reduction of the carbonyl group.

Examples

100 g. of acetone are completely hydrogenated in 10 minutes with 1 g. of copper chromite at 150°C. and 100 to 150 atmospheres. Isopropyl alcohol, the only product of the reaction, is formed in quantitative yield.[22]

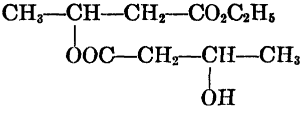
Pinacolone (200 g.) gives a quantitative yield of 3,3-dimethyl-2-butanol with 5 g. of copper chromite after 78 minutes at 150°C. and 100 to 150 atmospheres.[22]

77 g. of furfural are hydrogenated to furfuryl alcohol at 150°C. and 100 atmospheres in 5 minutes with 2 g. of copper chromite. The yield is 97%.

76 g. of camphor ($[\alpha]_D = +46.5°$) are hydrogenated quantitatively to optically active α-isoborneol ($[\alpha]_D = -22°$) with 6 g. of copper chromite in 1 hour at 120°C. and 150 to 200 atmospheres.[24]

When a solution of 18 g. of glucose in 60 ml. of 95% ethanol is hydrogenated with 1 g. of copper chromite at 160°C. and 170 atmospheres, the reduction is complete in 4 hours. The yield of sorbitol amounts to 97% of the theoretical quantity.[23]

50 g. of ethyl acetoacetate in ethanol solution, after 3 hours at 150°C. and 100 to 150 atmospheres with 1 g. of copper chromite, give a 97% yield of ethyl β-hydroxybutyrate. If the hydrogenation is conducted in the absence of a solvent, the yield of ethyl β-hydroxybutyrate is only 77%; in addition, there is formed 7% of dehydroacetic acid and 16% of ethyl β-(β'-hydroxybutyryloxy)butyrate:



$$\begin{array}{l} CH_3-\underset{\displaystyle |}{CH}-CH_2-CO_2C_2H_5 \\ \quad\;\; OOC-CH_2-\underset{\displaystyle \overset{|}{OH}}{CH}-CH_3 \end{array}$$

of which the latter owes its formation to a transesterification reaction that is suppressed by ethanol.

Ethyl methyloxalacetate (202 g.) is hydrogenated with 15 g. of copper chromite in 300 ml. of ethanol at 200°C. and 200 to 300 atmospheres in 14 hours. The yield of ethyl α-hydroxy-β-methylsuccinate is 90%.[25]

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[24] Bowden and Adkins, *J. Am. Chem. Soc.*, **56**, 689 (1934).

$$C_2H_5OOC{-}CO{-}\underset{CH_3}{\underset{|}{CH}}{-}COOC_2H_5 + H_2 \longrightarrow C_2H_5OOC{-}CHOH{-}\underset{CH_3}{\underset{|}{CH}}{-}COOC_2H_5$$

50 g. of mesityl oxide are hydrogenated with 2 g. of copper chromite at 175°C. and 100 to 150 atmospheres in 7 hours to yield 97% of the theoretical amount of methylisobutylcarbinol.

4. Reduction of Carboxylic Esters to Alcohols

In all of the reductions described in the foregoing paragraphs similar results may be obtained by use of nickel catalysts. However, the reduction of carboxylic acids, in the form of their esters, to the corresponding primary alcohols is a unique function of the copper chromite catalyst. This method competes favorably, both from the standpoint of yields and ease of manipulation, with the older method of Bouveault and Blanc, which involves the use of sodium and alcohol. Until recent years the latter method was the only way known by which such a transformation could be effected. In only one instance is Bouveault's method superior; that is, when it is desired to reduce an unsaturated ester with complete retention of the double bond or bonds. It is a well known fact that the alkene linkage is not subject to attack by sodium and alcohol provided it is not conjugated with a carbonyl or carboxyl group. By variation of the Adkins catalyst some success has been achieved toward retention of the double bond in catalytic reductions; this will be described later in the section devoted to selective hydrogenation.

In general, the reduction of a carbalkoxy group with copper chromite requires the use of high temperatures and high hydrogen pressures, usually about 200° to 250°C. and 200 to 300 atmospheres. Esters of monocarboxylic acids as a rule react smoothly and give very good yields of primary alcohols. Ethyl succinate and its higher homologues likewise give good results. Ethyl oxalate, because of lack of practical interest, has not yet been investigated, and the reduction of malonic ester and its derivatives, as well as the esters of certain aryl-substituted acids, offers difficulties which will be considered below.

The wide scope of the method is illustrated in Table I; all the reductions were carried out with copper chromite at a temperature of 250°C. and a pressure of 200 to 300 atmospheres of hydrogen. In conjunction with Table I the preparation of hexamethylene glycol from ethyl adipate, according to the directions of Lazier, Hill, and Amend,[26] will be described in detail. The procedure can be readily adapted to the hydrogenation of other esters.

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[25] Wojcik and Adkins, *J. Am. Chem. Soc.*, 55, 4939 (1933).

[26] Blatt, ed., *Organic Syntheses*, Wiley, New York, 1943, Coll. Vol. II, p. 325.

TABLE I

Hydrogenation of Esters to Primary Alcohols

Ester	Quantity, g.	Time, hrs.	Catalyst, g	Product	Yield, %
Ethyl valerate	35	5	5	1-Pentanol	94
Butyl caproate	35	0 6	5	1-Hexanol	95
Ethyl caprylate	42	6	6	1-Octanol	94
laurate	228	4	15	1-Dodecanol	97
myristate	64	2	5	1-Tetradecanol	98
stearate	130	3	7	1-Octadecanol	95
α-methylbutyrate	15	1 8	3	2-Methyl-1-butanol	97
pivalate	260	8	20	*tert*-Butylcarbinol	88
lactate	30	3 5	5	1,2-Propanediol	90
cinnamate	75	3	6	3-Phenyl-1-propanol	93
succinate	870	1 5	30	1,4-Butanediol	74
				Butyrolactone	18
α-methylsuccinate	110	0 7	16	2-Methyl-1,4-butanediol	72
glutarate	38	1 8	7	1,5-Pentanediol	95
adipate	500	9	20	1,6-Hexanediol	95
Diethyl dodecamethylene dicarboxylate	200	4	15	1,14-Tetradecanediol	95

HEXAMETHYLENE GLYCOL. In a steel bomb of at least 400 ml. capacity are placed 252 g. (1.25 moles) of ethyl adipate and 20 g. of copper chromite catalyst, prepared either with or without the addition of barium as described above. The bomb is closed, secured in a suitable agitating device,[27] and hydrogen introduced. The pressure to be used must be well within the capacity of the reaction vessel. It must be remembered that the final pressure, because of the high temperature which must be attained, is about 1.8 times greater than the original pressure. The original pressure of hydrogen should not exceed 140 atmospheres if the maximum working pressure of the bomb is 350 atmospheres. If the working pressure is 650 to 700 atmospheres, as much as 200 atmospheres of hydrogen can be applied at room temperature.

Agitation is started, and the reaction vessel is heated as rapidly as possible to 255°C. The temperature is maintained at 255°C. until the gage no longer shows a drop in pressure during a 1 hour period. The hydrogenation is complete in 6 to 12 hours, depending on the activity of the catalyst, the pressure of hydrogen, and the purity of the ester used. Unless a high pressure of hydrogen is used originally, or the reaction vessel is of large capacity (2 liters), it will be necessary to introduce more hydrogen during the reaction to maintain the pressure above 100 atmospheres.

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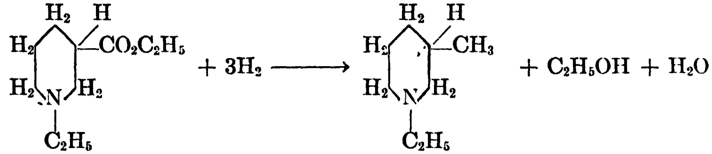
[27] A high pressure autoclave, equipped with a stirrer, could be used; however, for organic laboratories which only occasionally carry out high pressure hydrogenations the author recommends the purchase of a rocking or rotating bomb. The stirrer on an autoclave is apt to be a continual source of trouble, since it tends to develop leaks at the stuffing box unless the apparatus is under constant expert care.

When the reaction is complete, the vessel is cooled, the pressure released, and the contents transferred to a 600 ml. beaker with the aid of four 25 ml. portions of 95% ethanol. The catalyst is removed by filtration, or better by centrifuging, and washed with four more 25 ml. portions of 95% ethanol.[28] To the filtrate are added 50 ml. of 40% aqueous sodium hydroxide and the solution is boiled under reflux for 2 hours. The reaction product then is placed in a 1 liter distilling flask and the alcohol removed by distilling to a vapor temperature of 95°C. The hot residue is transferred to an apparatus for the continuous extraction of liquids, 50 ml. of water being used to rinse the flask. The liquid is extracted exhaustively with ether or benzene. This process requires from 24 to 50 hours, depending upon the efficiency of the apparatus. The solvent then is distilled, and after removal of the alcohol and water the glycol is distilled under reduced pressure from a 250 ml. Claisen flask. The yield is 125 to 132 g., corresponding to 85 to 90% of the theoretical amount; b.p. 143° to 144°C. (4 mm.); m.p. 41° to 42°C.

The reduction of the carbalkoxy to the carbinol group usually is unsuccessful when a phenyl, pyridyl, piperidyl, or pyrryl ring is in the position α to the carbalkoxy group. In such cases the reduction proceeds further with elimination of oxygen to form a methyl group. Examples of this type of reaction have been given on page 111.

In this connection it might be noted that ethyl *N*-ethylnipecotinate yields under standard conditions 99% of the theoretical amount of 1-ethyl-3-methylpiperidine.



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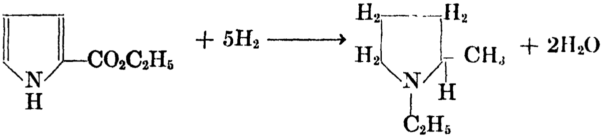
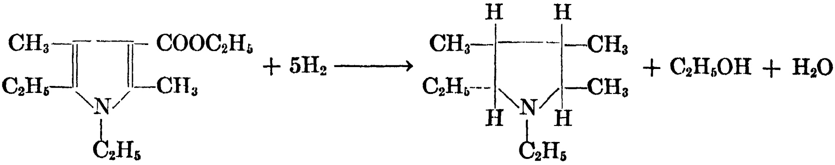
[28] In the preliminary experiments on a new compound, determination of the saponification number of the crude reduction product will indicate whether the catalyst was active and the pressure and temperature were chosen correctly. If the crude product is very pure, the glycol can be isolated by fractional distillation at this stage. A simpler method than that described above for the purification of the crude ester-containing hexamethylene glycol is recommended by Burks and Adkins, *J. Am. Chem. Soc.*, **62**, 3300 (1940): 30 g. of crude glycol, with an ester content of about 1%, are dissolved in 50 ml. of water and shaken with four 50 ml. portions of benzene. The water solution is then distilled through a modified Widmer column *in vacuo*, whereby 93% of the original crude product is obtained in pure form.

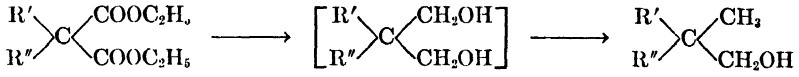
The hydrogenation of numerous pyrrolecarboxylic esters also has been investigated.[19,29] Thus, 2-carbethoxypyrrole was found to undergo a simultaneous hydrogenation of the pyrrole nucleus, followed by alkylation of the ring nitrogen by the alcohol formed by reduction of the carbethoxy group, to yield 90% of the theoretical amount of 1-ethyl-2-methylpyrrolidine.



In like manner, 3-carbethoxy-1,5-diethyl-2,4-dimethylpyrrole yields 88% of 1,5-diethyl-2,3,4-trimethylpyrrolidine.

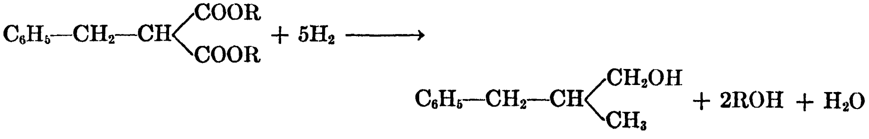


The reaction also takes an abnormal course with malonic ester and its derivatives.[22] Substituted malonic esters undoubtedly are first transformed into the normal products, 1,3-glycols; but, as noted on page 111, these glycols readily undergo further reduction to primary alcohols under the conditions necessary to reduce the ester linkage.



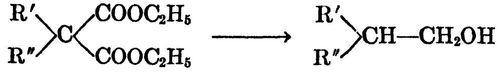
$$\begin{matrix}R' \\ R''\end{matrix}\!>\!C\!<\!\begin{matrix}COOC_2H_5 \\ COOC_2H_5\end{matrix} \longrightarrow \left[\begin{matrix}R' \\ R''\end{matrix}\!>\!C\!<\!\begin{matrix}CH_2OH \\ CH_2OH\end{matrix}\right] \longrightarrow \begin{matrix}R' \\ R''\end{matrix}\!>\!C\!<\!\begin{matrix}CH_3 \\ CH_2OH\end{matrix}$$

Malonic ester, itself, yields n-propyl alcohol with some ethyl propionate as by-product. From ethyl benzylmalonate 68% of the theoretical amount of 2-benzyl-1-propanol is obtained.



$$C_6H_5—CH_2—CH\!<\!\begin{matrix}COOR \\ COOR\end{matrix} + 5H_2 \longrightarrow C_6H_5—CH_2—CH\!<\!\begin{matrix}CH_2OH \\ CH_3\end{matrix} + 2ROH + H_2O$$

Still another side reaction sometimes is observed with substituted malonic esters; a carbalkoxy group may be eliminated completely with formation of the corresponding primary alcohol.



$$\begin{matrix}R' \\ R''\end{matrix}\!>\!C\!<\!\begin{matrix}COOC_2H_5 \\ COOC_2H_5\end{matrix} \longrightarrow \begin{matrix}R' \\ R''\end{matrix}\!>\!CH—CH_2OH$$

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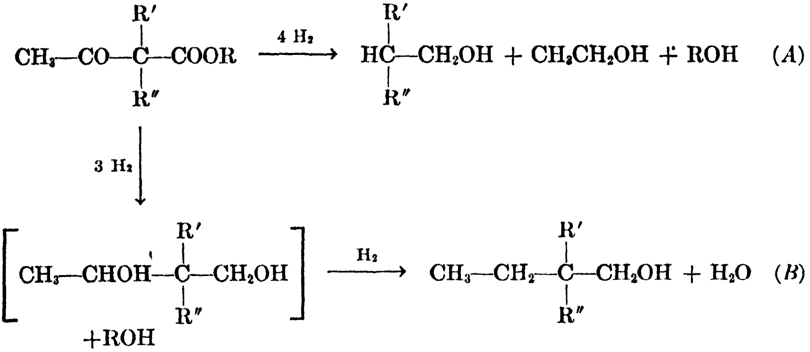
[29] Signaigo and Adkins, *J. Am. Chem. Soc.*, 58, 1122 (1936).

Thus, from ethyl dimethylmalonate ($R' = R'' = CH_3$) 88% of the theoretical amount of isobutyl alcohol is formed.

Hydroxy and keto esters usually can be reduced to the corresponding glycols if these substituents are not in the β-position with respect to the ester linkage; otherwise, the unstable 1,3-glycols again are formed. In the hydrogenation of substituted β-keto esters still another reaction occurs which is analogous to the well known acid cleavage of these compounds.



$$CH_3—CO—\overset{R'}{\underset{R''}{C}}—COOR \xrightarrow{4\ H_2} H\overset{R'}{\underset{R''}{C}}—CH_2OH + CH_3CH_2OH + ROH \quad (A)$$

$$\downarrow 3\ H_2$$

$$\left[CH_3—CHOH—\overset{R'}{\underset{R''}{C}}—CH_2OH\right] + ROH \xrightarrow{H_2} CH_3—CH_2—\overset{R'}{\underset{R''}{C}}—CH_2OH + H_2O \quad (B)$$

Whether and to what extent the reaction proceeds according to course *A* or *B* depends largely on the nature of the substituents, R′ and R″. However, the experimental data thus far accumulated are insufficient for the formulation of a generally valid rule.[22,25]

5. Reduction of Amides to Amines

The hydrogenation of amides to amines requires the use of rigorous conditions. In general, the reaction must be carried out under 200 to 300 atmospheres of hydrogen at 250° to 265°C. in the presence of at least 15% of copper chromite (based on the weight of amide). According to the equation:

$$R—CONH_2 + 2H_2 \longrightarrow R—CH_2—NH_2 + H_2O$$

water is formed, which at the high temperatures used tends to saponify the amide.

$$R—CONH_2 + H_2O \longrightarrow R—COOH + NH_3$$

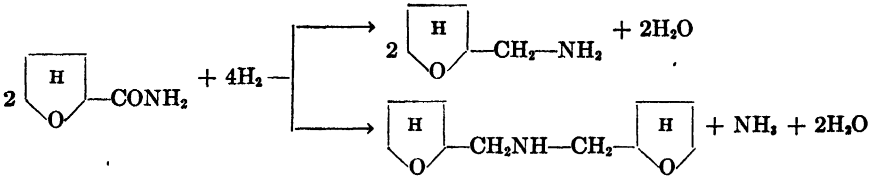
The acid thus formed impairs the activity of the catalyst. This side reaction is best avoided by the use of dioxane as a solvent (about 350 to 400 ml. per mole of amide), thereby inducing the reaction to run as rapidly as possible. Good yields of amine are obtained only if the hydrogenation of 0.5 to 0.2 mole of amide is complete within 1 hour.

The yield of amines is in most instances satisfactory; however, in the hydrogenation of unsubstituted amides the product always consists of a mixture of the primary and secondary amine in which the latter, the less desirable product, frequently predominates. With disubstituted amides, in which alkylation of the product is not possible, the tertiary amine is formed in excellent yield as the sole product of the reaction.[30]

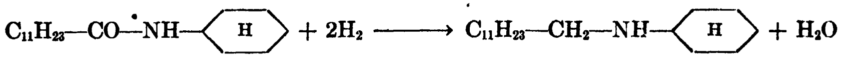
Lauramide, under the prescribed conditions, produces a mixture of approximately equal amounts of *n*-dodecylamine and di-*n*-dodecylamine for a total yield of 97% of the theoretical amount.

From heptamide is obtained a 39% yield of *n*-heptylamine and 58% of di-*n*-heptylamine.

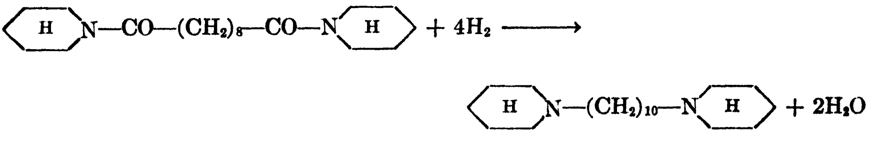
From tetrahydrofuroamide is formed 60% of the theoretical amount of tetrahydrofurfurylamine and 33% of ditetrahydrofurfurylamine.



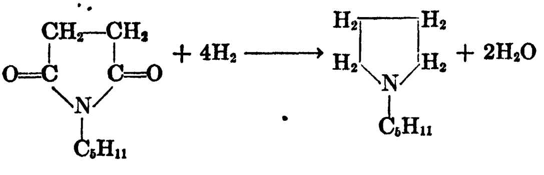
N-Cyclohexyllauramide produces cyclohexyl-*n*-dodecylamine in 62% yield, along with smaller amounts of di-*n*-dodecylamine, cyclohexylamine, and dicyclohexylamine.



The di-*N*-pentamethyleneamide of sebacic acid yields 94% of 1,10 dipiperidinodecane.



Cyclic amides (lactams) and imides likewise can be reduced by this method; for example, *N*-amylsuccinimide yields 88% of the theoretical amount of *N*-amylpyrrolidine.



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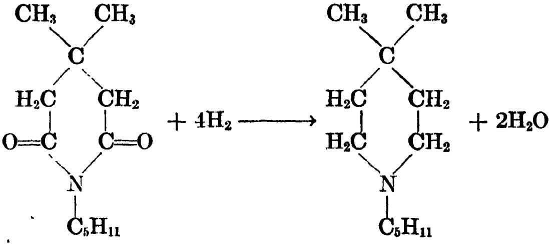
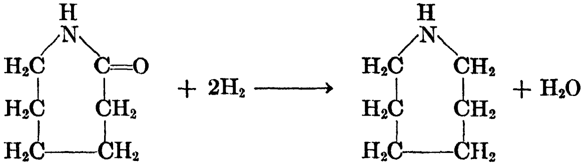
[30] Wojcik and Adkins, *J. Am. Chem. Soc.*, **56**, 2419 (1936).

Also, *N*-amyl-β,β-dimethylglutarimide yields 67% of 1-amyl-4,4-dimethylpiperidine, in addition to 7% of 4,4-dimethylpiperidine and 11% of the unchanged imide.



The hydrogenation of ε-caprolactam leads primarily to hexamethylenimine; some hexamethylenediamine also is formed.[31]



Hydroxyamines can be prepared successfully from hydroxy or keto amides provided these substituents are not in the β position with respect to the amide group; otherwise, they are replaced by hydrogen.[32]

6. Reduction of Other Nitrogen-Containing Compounds

Apparently, copper chromite can also be used as catalyst for the reduction of aromatic nitro compounds, but it offers no advantages over the nickel catalysts. 75 g. of nitrobenzene were reduced in the presence of 3 g. of copper chromite to aniline in 98% yield. The reaction took place in 42 minutes at a temperature of 175°C. and a pressure of 100 to 150 atmospheres. Likewise, *m*-dinitrobenzene was converted to *m*-phenylenediamine in 70% yield.[4] These same reactions can be carried out over nickel catalysts at about 100°C

For the reduction of other nitrogen-containing compounds, such as nitriles, oximes, and imines, to the corresponding amines copper chromite is of no value; these reactions are best carried out over nickel or the noble metal catalysts.

V. SELECTIVE HYDROGENATION

Any consideration of the question of selective hydrogenation in this chapter must be limited essentially to those problems which can be solved with copper chromite alone by variation of reaction time, temperature, pressure, concentration, and solvent.

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[31] French Patent, 860,398 (1940).

[32] D'Ianni and Adkins, *J. Am. Chem. Soc.*, **61**, 1675 (1939).

The control of the reaction time is often a useful means of achieving selective hydrogenation. For example, ethyl phenylacetate is reduced at 250 °C. to β-phenylethanol:

$$C_6H_5—CH_2—CO_2C_2H_5 + 2H_2 \xrightarrow{250°C.} C_6H_5—CH_2—CH_2OH + C_2H_5OH$$

but at this same temperature β-phenylethanol is converted to ethylbenzene.

$$C_6H_5—CH_2—CH_2OH + H_2 \xrightarrow{250°C} C_6H_5—CH_2—CH_3 + H_2O$$

Accordingly, the optimum yield of β-phenylethanol is obtained only when the reaction is interrupted before hydrogenation of the ester to the alcohol is complete.[23]

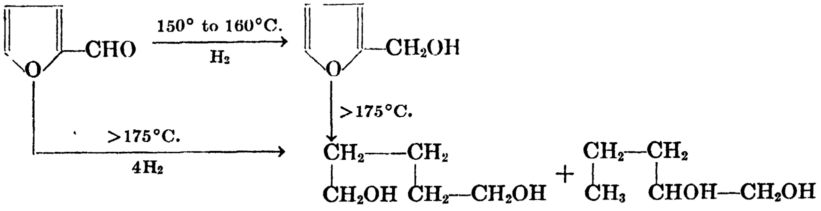
Likewise, the hydrogenation of ethyl succinate must be discontinued at an opportune moment, if a good yield of tetramethylene glycol is desired. The glycol is formed first:

$$C_2H_5O_2C—CH_2—CH_2—CO_2C_2H_5 + 4H_2 \xrightarrow{250°C} HOCH_2—CH_2—CH_2—CH_2OH + 2C_2H_5OH$$

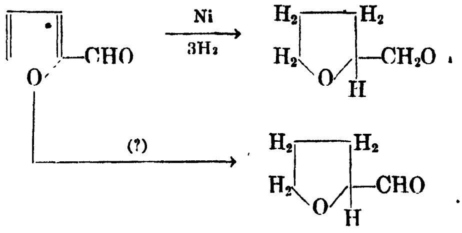
and is transformed under the prevailing conditions, although more slowly, to 1-butanol.[25]

$$HOCH_2—CH_2—CH_2—CH_2OH + H_2 \longrightarrow CH_3—CH_2—CH_2—CH_2OH + H_2O$$

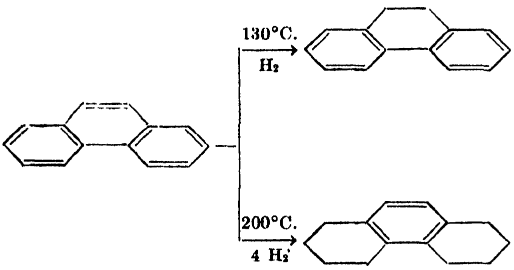
The temperature often exerts a directive influence on the course of a reaction. A good example is the hydrogenation of furfural. At 150° to 160 °C. furfuryl alcohol is formed in quantitative yield. If the hydrogenation of furfural or furfuryl alcohol is carried out above 175 °C., cleavage of the ring occurs with the formation of 1,2-pentanediol and 1,5-pentanediol.

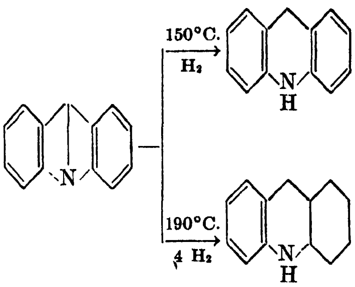


It might also be pointed out that of the other possible variations in the reduction of furfural, hydrogenation to tetrahydrofurfuryl alcohol requires the use of nickel catalysts, while for the direct conversion of furfural into tetrahydrofurfural no catalyst has yet been found.



The selective hydrogenation of various aromatic nuclei is also dependent upon the temperature. Phenanthrene is reduced at 130 °C. to 9,10-dihydrophenanthrene, and at 200 °C. to 1,2,3,4,5,6,7,8-octahydrophenanthrene.[17] Acridine gives a 90% yield of 9,10-dihydroacridine at 150 °C., while at 190 °C. *as*-octahydroacridine is formed in 70% yield.[33]





Adkins has shown that the carbalkoxy group in esters of unsaturated acids, such as oleic acid, can be reduced with retention of the double bond.[34] In this case, however, it is necessary to replace the copper chromite catalyst with zinc chromite[35] which is less active toward the double bond. Zinc chromite, on the other hand, requires the use of higher temperatures (290° to 300 °C.).

In the hydrogenation of 60 g. of butyl oleate with 50 g. of zinc chromite a 65% yield of oleyl alcohol was obtained after 11 hours.

$$CH_3-(CH_2)_7-CH{=}CH-(CH_2)_7-CO_2C_4H_9 + 2H_2 \xrightarrow[300°C.]{ZnCrO}$$

$$CH_3-(CH_2)_7-CH{=}CH-(CH_2)_7-CH_2OH + C_4H_9OH$$

Likewise, 50 g. of butyl erucate were reduced with 26 g. of zinc chromite in $6^1/_2$ hours. The yield of 13-docosen-1-ol was 68%.

The last two reactions which have been considered cannot be carried out with copper chromite; therefore, strictly speaking, they are outside the scope of this chapter. They are presented here as illustrations of the fact that, in the last analysis, the real problem of selective hydrogenation is the need for more specific catalysts. As a rule, such catalysts tend to be adjusted to the "substrate," almost like an enzyme, and often fail to work even on closely related compounds.

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[33] Adkins and Coonradt, *J. Am. Chem. Soc.*, **63**, 1563 (1941).

[34] Sauer and Adkins, *J. Am. Chem. Soc.*, **59**, 1 (1937); see also S. Komori, *Chem. Abstracts*, **35**, 1758 (1941).

[35] This catalyst is prepared by a procedure analogous to that described for copper chromite.

The ultimate goal of the organic chemist in the field of catalytic hydrogenation will have been reached only when there exists a hydrogenation catalyst specific for each of the various functional groups. The progress made in this direction in the field of oxidation of organic compounds leads to the expectation that this goal will be approached much more closely in the course of time.

The Meerwein-Ponndorf Reduction and Oppenauer Oxidation

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Translated and revised by ELEANOR R. WEBSTER *and* JEAN V. CRAWFORD

I. INTRODUCTION

The reversible transformation between carbonyl and hydroxyl compounds in the presence of metallic alkoxides discovered by Meerwein and Schmidt,[1] Oppenauer,[2] and others has been extensively employed for the preparation of a wide variety of compounds.[3]

The pairs of compounds, aldehydes-primary alcohols and ketones-secondary alcohols, constitute oxidation-reduction systems of different potentials[4] and different reaction velocities. A dynamic homologous series is involved whose members, such as quinone-hydroquinone[5] and thiol-disulfide,[6] are subject to similar rules. The difference in reaction velocity between two such systems is small or equal to zero; however, a reaction can be forced if an oxidation-reduction catalyst which reacts spontaneously with both systems can be found. The metallic alkoxides are such catalysts for the carbonyl-hydroxyl system, and in practice the aluminum alkoxides have proved especially useful because of certain advantageous characteristics. The velocity with which the equilibrium represented by the equation

$$\mathrm{RCOR'} + \mathrm{R''CH(Oal^*)R'''} \rightleftharpoons \mathrm{RCH(Oal)R'} + \mathrm{R''COR'''}$$

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* The symbol "al" is used instead of Al/3 to represent an equivalent weight of aluminum.

[1] Meerwein and Schmidt, *Ann.*, **444**, 221 (1925). The first reductions of this type (reported by Luttringhaus, German Patent, 384,351; *Chem. Zentr.*, **1924**, **I**, 2398) made use of magnesium, iodine, and alcohol. Probably alkoxides are the effective catalysts, but the method did not come into use, since the resulting alkoxide produces resinification with unsaturated aldehydes.

[2] Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937). *Cf.* Inhoffen, Logemann, Hohlweg, and Serini, *Ber.*, **71**, 1024 (1938), in which the use of aluminum isopropoxide was recommended in place of aluminum *tert*-butoxide for the purpose of oxidation.

[3] A recent review of the Meerwein-Ponndorf reaction has been published by Wilds in *Organic Reactions*, Wiley, New York, 1944, Vol. II, pp. 178–223.

[4] Adkins and Cox, *J. Am. Chem. Soc.*, **60**, 1151 (1938). Cox and Adkins, *ibid.*, **61**, 3364 (1939).

[5] Dimroth, *Angew. Chem.*, **46**, 571 (1933).

[6] Bersin and Steudel, *Ber.*, **71**, 1015 (1938).

can be established depends primarily upon the oxidation-reduction potential of both pairs of compounds[7]:

RCOR′ and RCHOHR′ and R″COR‴ and R″CHOHR‴

Secondary alcohols are, in general, better suited for the reduction of ketones,[7,8] since the potentials of the different pairs of ketones-secondary alcohols are of the same order of magnitude and thus the concentrations do not vary appreciably from a 1:1 ratio in equilibrium. Experimentally an excess either of the carbonyl or of the hydroxyl compound is used, according to the result to be obtained, and one of the reaction products is removed as completely as possible by distillation in order to displace the equilibrium of the reversible reaction.

The relative reactivity of different ketones was determined by Cox and Adkins[4] by the polarographic method. The oxidation potentials listed in Table I are given in reverse order to the corresponding reduction potentials.

TABLE I

Cyclohexanone	(0.19)	*tert*-$C_4H_9\cdot CO\cdot C_6H_5$	0.64
$C_6H_5\cdot CO\cdot C_6H_5$	0.32	$C_2H_5\cdot CO\cdot C_2H_5$	0.68
i-$C_3H_7\cdot CO\cdot C_6H_5$	0.39	*i*-$C_4H_9\cdot CO\cdot$*i*-C_4H_9	(0.93)
$C_2H_5\cdot CO\cdot C_6H_5$	0.51	*n*-$C_3H_7\cdot CO\cdot$*n*-C_3H_7	0.95
n-$C_5H_{11}\cdot CO\cdot C_6H_5$	0.52	*n*-$C_4H_9\cdot CO\cdot$*n*-C_4H_9	0.97
n-$C_4H_9\cdot CO\cdot C_6H_5$	0.55	*i*-$C_3H_7\cdot CO\cdot$*i*-C_3H_7	1.00
n-$C_3H_7\cdot CO\cdot C_6H_5$	0.62		

In this series the most powerful oxidizing agents are at the top, the least active at the bottom. The corresponding secondary alcohols may be arranged in the same order, but they function in the opposite way, diisopropylcarbinol being the strongest reducing agent and cyclohexanol the weakest. These facts are in accord with the results obtained in oxidation and reductions with alkoxides.

The catalytic action of the aluminum alkoxide is attributed to the fact that the alcohol develops the necessary reaction velocity with the ketone only in the form of the aluminum compound. Since the oxidizing alcohol HOR′ must be present in the reaction mixture as $Al(OR')_3$, it is advantageous to add a previously prepared alkoxide $Al(OR)_3$. In the Oppenauer oxidation this added alkoxide should be that of a tertiary alcohol, since otherwise it may be oxidized in the reaction mixture.

Isopropyl alcohol and ethyl alcohol have proved useful as reducing agents in many cases, while acetone and cyclohexanone[9] have generally been used for the oxidation of costly alcohols of the steroid series.

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[7] Lund, *Ber.*, **70**, 1520 (1937).

[8] Meerwein, Bock, Kirschnick, Lenz, and Migge, *J. prakt. Chem.*, **147**, 211 (1936).

[9] However, both ketones exhibit a strong tendency to condense. Recently Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940), has recommended the use of benzoquinone

It is not the purpose of this review to describe the different theoretical interpretations of the reaction mechanism in the oxidation-reduction of hydroxyl and carbonyl compounds.[8,10,11] As Meerwein[8] implies, electron and proton exchanges between molecular complexes are unquestionably important elements. According to Ponndorf,[11] three contributing factors are (*a*) the ease with which the alcohols lose hydrogen, (*b*) the absorptivity of the double bond of the carbonyl compound for hydrogen, and (*c*) the tendency of the alcohols to form metal alkoxides. Lund[7] and Oppenauer[2] point out the importance of solubility and of varying decomposition tendencies of the resulting intermediate molecular complexes. Recently Davies and Hodgson[12] have postulated that the function of the aluminum alkoxide is to activate one of the alcoholic hydrogen atoms for the purpose of hydrogen bonding rather than to facilitate the replacement of one alkoxyl group in the aluminum alkoxide by another.

The preparative importance of the aluminum alkoxides as catalysts in the oxidation-reduction between hydroxyl and carbonyl compounds has been conclusively established. With the help of such catalysts sensitive unsaturated or halogenated aldehydes and ketones can be converted into the corresponding alcohols in good yield. These alkoxides have often replaced chromic acid which had been used almost exclusively for the oxidation of unsaturated hydroxy steroids.[13]

II. MEERWEIN-PONNDORF REDUCTION OF CARBONYL COMPOUNDS

1. General Considerations

Primary alcohols and the corresponding aluminum alkoxides are best suited for the reduction of aldehydes. The aluminum compounds of secondary alcohols have proved better for certain aldehydes which are reduced with difficulty.

Halogenated aliphatic aldehydes which are satisfactorily reduced by aluminum alkoxides are catalytically cleaved by chloromagnesium ethoxide; for instance, chloral yields the ester of formic acid in addition to carbon monoxide and chloroform. For the reduction of sensitive aldehydes such as crotonaldehyde with chloromagnesium ethoxide, the concentration of the catalyst must be smaller than usual and it is advisable to use an excess of magnesium ethoxide for protection against any trace of water present.

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[10] Verley, *Bull. soc. chim.*, 37, 871 (1925).

[11] Ponndorf, *Angew. Chem.*, 39, 138 (1926).

[12] Davies and Hodgson, *J. Soc. Chem. Ind.*, 62, 109 (1943).

[13] For the use of metallic alkoxides in the reduction of steroids see also Societé pour l'industrie chimique à Bâle, French Patent, 847,134, October 3, 1939 [*Chem. Abstracts*, 35, 5653 (1941)]; Windaus and Schenck, German Patent, 701,601, December 19, 1940 [*Chem. Abstracts*, 35, 7976 (1941)].

In a series of thirty experiments Young, Hartung, and Crossley[14] investigated the influence of such factors as solvent, reaction time, temperature, and concentration. In the reduction of crotonaldehyde with aluminum isopropoxide the yields obtained with *m*-xylene or benzene as solvent were smaller than with excess isopropyl alcohol. Since Young *et al.* observed that the greatest difficulty in carrying out the Meerwein-Ponndorf reduction results from polymerization of the carbonyl compounds present, especially if acetaldehyde is formed as a reaction product, they recommend the use of a secondary alkoxide oxidizing to a ketone rather than a primary alkoxide yielding an aldehyde. The extent of polymerization may be minimized by removal of the ketone formed or by increasing the proportion of solvent. The latter procedure is not advisable, because the reaction rate is decreased markedly with a decrease in the concentration of the material to be reduced. In order to repress polymerization, it is better to use the alkoxide in excess of the calculated quantity. Schmidt[15] observed polymerization when treating isocitral for more than fourteen hours with aluminum alkoxide. The American workers have[14] reported that the increase in yield of desired alcohol which could be obtained by increasing the reaction time was often offset by an increase in the amount of polymerization. Lund[7] has pointed out that the optimum reaction times for reduction with aluminum isopropoxide differ considerably with different carbonyl compounds. The reaction proceeds very slowly in the case of camphor and very rapidly with most aldehydes and with simple ketones such as cyclohexanone.

Meerwein[8] states that phenolic aldehydes are more satisfactorily reduced if they have been previously methylated. Helferich and Frick[16] report that aliphatic hydroxy aldehydes react with difficulty because of the formation of acetals.

For reducing carotenoid ketones by means of aluminum isopropoxide, Karrer and Solmssen[17] recommend the use of comparatively small quantities of material, as in the reduction of dihydrorhodoxanthine for which the procedure is given on pages 134–135.

The reduction of hydroaromatic ketones yields mixtures of the *cis* and *trans* alcohols, but the isomers are not necessarily formed in equal quantities. Gillespie, Macbeth, and Swanson[18] found the formation of *trans*-*l*-cryptol to be predominant in the reduction of *l*-cryptone:

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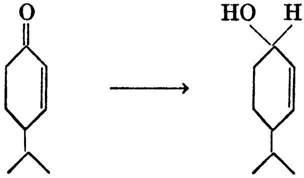
[14] Young, Hartung, and Crossley, *J. Am. Chem. Soc.*, 58, 100 (1936).

[15] Schmidt, *Ber. Schimmel and Co.*, 1939, 114.

[16] Helferich and Frick, *Ber.*, 58, 1246 (1925).

[17] Karrer and Solmssen, *Helv. Chim. Acta*, 18, 477 (1935). Karrer and Hübner, *ibid.*, 19, 476 (1936).

[18] Gillespie, Macbeth, and Swanson, *J. Chem. Soc.*, 1938, 1820. Cooke, Gillespie, and Macbeth, *ibid.*, 1939, 518. Gillespie and Macbeth, *ibid.*, 1939, 1531.



The Meerwein-Ponndorf reduction has been found to yield a mixture of epimeric carbinols from every keto steroid to which it has been applied.[19] In reducing estrone by this method Marker and Rohrmann[20] obtained a mixture of α- and β-estradiol. In carrying out the reduction of androstene-3,17-dione by means of aluminum *tert*-butoxide in a mixture of *sec*-butyl alcohol and benzene, Miescher and Fischer[21] obtained *cis*- and *trans*-testosterone. Warming the mixture of isomers with concentrated hydrochloric acid destroys the *cis* form.

In certain cases the preparation of a desired epimer may be achieved by a combination of the Oppenauer oxidation and the Meerwein-Ponndorf reduction. Methyl 3(β)-hydroxy-17^{20}-pregnen-21-oate* was oxidized to the corresponding 3-keto compound which was then reduced, yielding some methyl 3(α)-hydroxy-17^{20}-pregnen-21-oate.[22] 3(α)-Hydroxy-17^{20}-allopregnen-21-oic acid was prepared by a similar transformation.[23]

According to an observation by Lund,[7] nitroso compounds may be reduced in certain circumstances, although nitro groups are not attacked by these reducing agents; however, a search of the literature does not reveal experimental details for such a reduction.

Meerwein[8] reported that both benzophenone and benzhydrol in the presence of aluminum ethoxide and ethyl alcohol were reduced to the hydrocarbon[24] with the simultaneous formation of acetic acid instead of acetaldehyde.[25]

Polyene ketones such as dibenzylideneacetone, cinnamylideneacetone, and others form ethers very readily in the presence of isopropyl alcohol.[14]

Reduction by means of aluminum alkoxides is not applicable to such ketones as acetoacetic ester, dibenzoylmethane, chelidonic acid ester, and others which have a strong tendency to enolize, as they form aluminum enolates which are not reduced. α-Benzylideneacetoacetic ester is hydrogenated easily, however. In the same way, phenolic ketones and ketonic acids whose aluminum salts are insoluble in isopropyl alcohol are not adapted to this type of reduction. However, quinone is easily reduced by means of isopropyl alcohol-aluminum isopropoxide even though the insoluble aluminum hydroquinone salt separates.

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* In this article the presence of a C—C double bond between carbons 17 and 20, for example, is indicated by 17^{20} instead of Δ^{17-20}.

[19] Marker, Turner, and Wittbecker, *J. Am. Chem. Soc.*, **64**, 221 (1942).

[20] Marker and Rohrmann, *J. Am. Chem. Soc.*, **60**, 2927 (1938).

[21] Miescher and Fischer, *Helv. Chim. Acta*, **22**, 158 (1939).

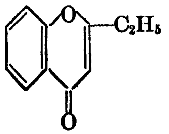
[22] Marker, Wagner, and Wittbecker, *J. Am. Chem. Soc.*, **64**, 2093 (1942).

[23] Marker, Crooks, Wagner, and Wittbecker, *J. Am. Chem. Soc.*, **64**, 2089 (1942).

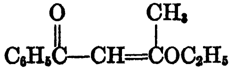
[24] Heilbron, Johnson, and Jones, *J. Chem. Soc.*, **1939**, 1560, report a single instance of the formation of a hydrocarbon in the aluminum isopropoxide reduction of axerophthylideneacetone.

[25] Diels and Rhodius, *Ber.*, **42**, 1072 (1909), observed the formation of an equivalent of isovaleric acid in the reduction of benzophenone to benzhydrol with amyl alcohol and its sodium alkoxide.

The failure of aluminum isopropoxide to reduce 2-ethylchromone may be accounted for by the fact that this ketone is an ester vinylogue.[26] Although esters undergo alkoxyl exchange with aluminum alkoxides, they are not reduced even under forcing conditions.[27] In order to determine whether open chain vinylogues approach more nearly the properties of esters and exhibit alkoxyl exchange, *O*-ethylbenzoylacetone and ethyl α-ethoxymethyleneacetoacetate were subjected to the action of aluminum isopropoxide in isopropyl alcohol.[28] Since neither reduction of the carbonyl group nor alkoxyl exchange was observed, Baker and Weiss[28] concluded that compounds which are open chain vinylogues of esters are too much like esters to be reduced by aluminum alkoxides but not sufficiently ester-like to undergo alkoxyl exchange.

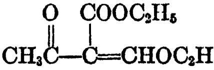


2-Ethylchromone



$C_6H_5\overset{O}{\overset{\|}{C}}-CH=\overset{CH_3}{\overset{|}{C}}OC_2H_5$

O-Ethylbenzoylacetone



$CH_3\overset{O}{\overset{\|}{C}}-\overset{COOC_2H_5}{\overset{|}{C}}=CHOC_2H_5$

Ethyl
α-ethoxymethyleneacetoacetate

Because 1,12-bisdiethylamino-2,11-diketododecane and 1,12-dipiperidino-2,11-diketododecane were not reduced by the Meerwein-Ponndorf method, Work[29] suggested that the carbonyl group must be conjugated with an unsaturated system in order to undergo reduction.

The number of successful Meerwein-Ponndorf reductions or Oppenauer oxidations of compounds containing basic nitrogen atoms is not great.[30] It is possible that the reactions fail because of the acidic nature of the catalyst, which may form complexes of the type $R_3\overset{+}{N}{=}\overset{-}{Al}R'_3$ in the presence of a base, thus effecting removal of the catalyst.[31] Suppression of the basic character of the nitrogen atom through salt formation has made possible the reduction of certain amino ketones in the form of their salts.[32] A modification of the Meerwein-Ponndorf procedure employing a basic catalyst, sodium isopropoxide in isopropyl alcohol, has brought about the satisfactory reduction of quininone to quinine. Woodward, Wendler, and Brutschy[31] investigated this modification because of the failure of the Oppenauer oxidation of quinine to quininone when aluminum *tert*-butoxide or aluminum phenoxide was used with a wide variety of ketones as oxidizing agents.

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[26] Baker and Schafer, *J. Am. Chem. Soc.*, **65**, 1675 (1943).

[27] Baker, *J. Am. Chem. Soc.*, **60**, 2673 (1938).

[28] Baker and Weiss, *J. Am. Chem. Soc.*, **66**, 343 (1944).

[29] Work, *J. Chem. Soc.*, 1940, 1315.

[30] For some examples of successful reductions of this type see especially the amino ketones listed in Table III, pages 138–141.

[31] Woodward, Wendler, and Brutschy, *J. Am. Chem. Soc.*, **67**, 1425 (1945).

2. Preparation of Reagents

A. Anhydrous Alcohols

In order to prepare absolute ethyl alcohol, 95% alcohol is refluxed 8 hours, protected from moisture, with slaked lime (500 g. to 1 liter), and is then distilled, finally under a slight vacuum. It is heated over metallic calcium, which is renewed after about 2 hours, and is distilled again into a dry flask. Density control through the use of a hydrometer is recommended. A similar procedure may be used for preparing anhydrous isopropyl alcohol. Gillespie and Macbeth[33] suggest the following method. Commercial isopropyl alcohol is stored over calcium oxide, and, as the material is needed, 2 liters are heated 2 hrs. with 5–10 g. of calcium under a reflux condenser protected by a drying tube. The alcohol is then distilled into a 2 liter flask containing some aluminum isopropoxide and immediately distilled again into a dry flask. Such a product dissolves aluminum powder in the presence of mercuric chloride when heated for 25 to 30 minutes.

The waste distillates from the Meerwein-Ponndorf reduction may be recovered for further use by heating for an hour with aluminum amalgam. However, the recovery of isopropyl alcohol must be carried out with caution.[34,35]

The necessary catalyst for the oxidation or reduction is best obtained by dissolving aluminum metal (in the form of wire, shavings, or powder) in the appropriate alcohol by refluxing. Since the aluminum is superficially coated with oxide, it is activated by treatment with iodine or mercuric oxide,[1,14] or by addition of an alkoxide prepared previously.[2] In many cases addition of absolute *sec*-butyl alcohol (2 ml. to 15 g. of aluminum[36]), magnesium ribbon (0.3 g. to 14 g. of aluminum[5]), or copper acetate[37] has proved useful. However, a smooth transformation is generally achieved if absolutely anhydrous alcohol is used, and if moisture is excluded by means of a drying tube during refluxing. Solution is obtained more readily with the higher boiling alcohols; with lower boiling alcohols, good results are secured by using inert solvents such as xylene in which the alkoxide is more soluble than in the alcohol itself. In many cases the reaction of an anhydrous metal chloride with a suitable alkali alkoxide[38] has been chosen for preparing the metal alkoxide. While the preparation of the most commonly used aluminum alkoxides will be described in detail only the reference to the method for obtaining chloromagnesium ethoxide is included.[39]

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[32] Drake and Goldman, *J. Org. Chem.*, **11**, 100 (1946).

[33] Gillespie and Macbeth, *J. Chem. Soc.*, **1939**, 1531.

[34] Wagner-Jauregg, *Angew. Chem.*, **52**, 709 (1939); see also Haussler, *ibid.*, **53**, 89 (1940).

[35] For a procedure effecting removal of peroxides from isopropyl alcohol distillates, see Wilds, in *Organic Reactions*, Wiley, New York, 1944, Vol. II, p. 198.

[36] Doeuvre, *Bull. soc. chim.*, **1**, 201 (1934).

[37] Short and Read, *J. Chem. Soc.*, **1939**, 1306.

B. Aluminum Isopropoxide, $Al(i\text{-}OC_3H_7)_3$

In a 2 liter round bottomed flask with a reflux condenser are placed 100 g. of aluminum, 1200 ml. of anhydrous isopropyl alcohol, and 5 g. of mercuric chloride. After warming the mixture for 10 to 20 minutes on the steam bath, a gray precipitate is formed, and such a vigorous reaction sets in that the flask must be cooled externally. Finally the reaction mixture is heated 6 to 7 hours, until the evolution of hydrogen has ceased. The excess isopropyl alcohol is distilled off, and the aluminum isopropoxide distilled *in vacuo*. The yield of isopropoxide boiling at 145° to 150°C. at 12 mm. is 85 to 90%.[7,14] In many cases the solution may be used directly.

C. Aluminum Ethoxide, $Al(OC_2H_5)_3$

100 g. of aluminum powder and 600 ml. of dry xylene are heated to boiling in a 2 liter flask fitted with a drop funnel and reflux condenser, and a solution of 0.5 g. each of mercuric chloride and iodine in 440 ml. of absolute ethyl alcohol is added dropwise. After the reaction starts, the heating source is removed for a short time. During the rapid addition of alcohol, the aluminum ethoxide containing alcohol of crystallization may separate; if this occurs, addition is interrupted momentarily. After 320 ml. of the alcohol solution have been introduced over a period of 40 minutes, heating is again resumed; and the rest is added over a period of 1.5 to 1.75 hours. The reaction mixture is heated 15 minutes longer, until the evolution of hydrogen has ceased. The hot mixture is then poured through a heated fluted filter, and the xylene is removed from the filtrate by distillation, the last portion *in vacuo*. The yield of aluminum ethoxide is 400 grams.[1]

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[38] Meerwein and Bersin, *Ann.*, **476**, 113 (1929). Verley, *Bull. soc. chim.*, **37**, 537, 871 (1925); **41**, 788 (1927).

[39] See also Schering, U. S. Patent, 2,170,124, August 22, 1939; *Chem. Zentr.*, **1940**, I, 1232; *Chem. Abstracts*, **34**, 1133 (1940).

D. Aluminum *tert*-Butoxide, $Al(tert\text{-}OC_4H_9)_3$

18 g. of aluminum amalgam and 100 g. of *tert*-butyl alcohol previously distilled over sodium are refluxed, while protected from moisture. The beginning of the reaction is evidenced by darkening of the mixture. In case the reaction does not start spontaneously, a trace of mercuric chloride or anhydrous alkoxide may be added. As soon as the evolution of hydrogen has stopped (about 12 to 15 hours), 500 ml. of benzene are added, the mixture is centrifuged, and the centrifugate concentrated *in vacuo* and warmed *in vacuo* at 100° for an hour.[2] The yield of butoxide is 75 to 90 g.[40] This butoxide is used principally for the oxidation of steroid alcohols.

3. Examples of Experimental Procedures

In many cases the reduction of aldehydes, furfural for example, may be effected without heating[1,41]; but in general this reaction is best carried out at higher temperatures. (Reductions with chloromagnesium ethoxide take place only under the latter condition.) The desired displacement of the equilibrium is achieved through the removal by distillation of the carbonyl compound formed (acetaldehyde or acetone). Experimental details are given for carrying out Meerwein's reduction of an aldehyde with ethyl alcohol-aluminum ethoxide and for the reduction of a ketone with isopropyl alcohol-aluminum isopropoxide as described by Ponndorf.

A. Reduction of Butyl Chloral

150 g. butyl chloral are dissolved in 400 ml. absolute ethyl alcohol; 45 g. aluminum ethoxide are added and the mixture refluxed in a stream of N_2 or H_2 (bath temp. 135°C.). To distil off the acetaldehyde, the reflux condenser is replaced with a fractionating column (60 × 6 cm.) packed with glass beads and jacketed with boiling methanol (see Hahn[42]). With larger runs the still head must be of correspondingly larger dimensions. The acetaldehyde distilling over is collected in two Péligot tubes, one containing alcohol and the other a solution of sodium bisulfite. From time to time the quantity of acetaldehyde formed is determined by Skrabal's[43] method. In a particular case 58.4% acetaldehyde in addition to 3% ethyl acetate and large quantities of acetal had formed after 14 hours. The alcohol is distilled off at the end (bath temperature 120°C.), the residue treated with 150 ml. of 2 *N* sulfuric acid, and steam-distilled. The product is filtered with suction and dried.[44]

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[40] For a similar preparation of aluminum *tert*-butoxide see Wayne and Adkins, *Org. Syntheses*, **21**, 8 (1941).

[41] Slotta and Lauersen, *J. prakt. Chem.*, **139**, 220 (1934).

[42] Hahn, *Ber.*, **43**, 420 (1910).

[43] Skrabal, *Z. physik. Chem.*, **111**, 98 (1924).

[44] The saponification of the ester formed as a side product yields an additional quantity of alcohol.

B. Reduction of Ketones

In a round bottomed flask fitted with an Allihn condenser packed with Raschig rings are placed 0.1 mole of the ketone and 60 ml. of a molar solution of aluminum isopropoxide in isopropyl alcohol. The cooling jacket is filled about two-thirds full with methanol. If many reductions are to be carried out, a fine capillary may be attached to the lower side tube with thick walled rubber tubing through which a thin stream of air is forced in order to insure even boiling of the methanol. The upper side tube of the jacket is connected to an ordinary reflux condenser, and the open end of the packed column is fitted with a thermometer and attached to another condenser set downward for distillation. The apparatus described permits most of the vapor of the alcohol being prepared to condense, while a mixture of acetone and isopropyl alcohol distils. By carrying out the distillation properly, the acetone is removed continually without carrying over too great a quantity of the desired alcohol. The process is identical when benzene is used as a solvent. The progress and end-point of the reaction are determined very simply by means of a solution of 2,4-dinitrophenylhydrazine in hydrochloric acid (1 g. in 1 liter of 2 *N* hydrochloric acid). When 5 ml. of this solution no longer give a precipitate with several drops of the distillate, the reaction may be considered complete. In order to be sure that the end-point has been reached, the reaction mixture is heated under total reflux for 5 to 10 minutes; and then distillation is started again and the first few drops coming over are tested with the reagent. If no precipitate appears, the complete formation of acetone is assured. The excess isopropyl alcohol is removed by distillation *in vacuo* and the aluminum complex is decomposed with dilute sulfuric acid or sodium hydroxide. Both the time of reaction and the final treatment of the product depend on the nature of the carbonyl and hydroxyl compounds involved.[7]

C. Reduction of Dihydrorhodoxanthine

65 mg. of dihydrorhodoxanthine are dissolved in 15 ml. benzene and 20 ml. absolute isopropyl alcohol. After the addition of 2 g. of aluminum isopropoxide the mixture is refluxed for 24 hours in a round bottomed flask fitted with a fractionating column packed with wire spirals. The temperature at the top of the column where a downward condenser is attached should not exceed 40°C., so that only a few milliliters of benzene are distilled over. A carefully purified stream of nitrogen is passed through the apparatus. After 24 hours, the reaction mixture is decomposed by warming with 20 ml. of 10% potassium hydroxide and extracted with ether. The ether extract is washed and dried, and the solvent is removed *in vacuo.* The residue, dissolved in benzene, is chromatographed through calcium hydroxide and eluted with benzene-methanol. The methanol is washed

out with water, the benzene distilled off *in vacuo*, and the product recrystallized from methanol. The yield of zeaxanthine is 8 mg. (12%).[17]

FOOTNOTES TO TABLES ON FOLLOWING PAGES

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[86] See also Organon, French Patent, 823,618; *Chem. Zentr.*, **1938**, **II**, 355; *Chem. Abstracts*, **32**, 5854 (1938). According to this patent, when dehydroandrosterone is heated with aluminum *tert*-butoxide in the presence of benzene without an oxidizing agent, a mixture of products is obtained among which are androstenedione, testosterone and 5-androstene-3,17-diol. See also Organon, Dutch Patent, 47,831, February 15, 1940; *Chem. Abstracts*, **34**, 6414 (1940).

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(*Footnotes to tables concluded on page 143*)

TABLE II

Reduction of Aldehydes

Compound reduced	Product formed	Reagent*	Per cent yield	Ref. No.
	Aliphatic			
Butyraldehyde	Butyl alcohol	C_2H_5	6	14
Citral	Geraniol Nerol	i-C_3H_7	36 —	14 11
Citronellal	Citronellol	i-C_3H_7	32	14
		CME	70–80	8
Hydroxycitronellal	Hydroxycitronellol	CME	78	8
11-Phenyl-2,4,6,8,10-undecapentaenal	11-Phenyl-2,4,6,8,10-undecapentaen-1-ol	i-C_3H_7	—	45
Vitamin A aldehyde	Vitamin A alcohol	i-C_3H_7	—	46
Bromal	Tribromoethyl alcohol	C_2H_5	69	1
		i-C_3H_7	77	7
Chloral	Trichloroethyl alcohol	C_2H_5	85	1, 47
2,2,3-Trichlorobutanal	2,2,3-Trichloro-1-butanol	C_2H_5	92	1
2-Bromo-2-butenal	2-Bromo-2-buten-1-ol	CME	—	8
2-Chloro-2-butenal	2-Chloro-2-buten-1-ol	CME	—	8
	Aromatic			
Benzaldehyde	Benzyl alcohol	CME	76	1
		C_2H_5	89	8
		$Zr(OC_2H_5)_4$	70	8
		$Sn(OC_2H_5)_4$	74	8
		$Ti(OC_2H_5)_4$	42	8
		i-C_3H_7	55	14

		Aromatic (*Continued*)		
4-Chlorobenzaldehyde	4-Chlorobenzyl alcohol	C_2H_5	92	1
2-Nitrobenzaldehyde	2-Nitrobenzyl alcohol	C_2H_5	92	7
4-Nitrobenzaldehyde	4-Nitrobenzyl alcohol	C_2H_5	92	1
		CME	70	8
4-Methoxybenzaldehyde	4-Methoxybenzyl alcohol	C_2H_5 (25°)	85	1
		CME	75	1
		$C_6H_5CH_2ONa$	—	11
Cumaldehyde	Cuminyl alcohol	*i*-C_3H_7	—	48
Cinnamaldehyde	Cinnamyl alcohol	C_2H_5	85.5	1, 49
		CME	80	1
		i-C_3H_7	68	14
		$C_6H_5CH_2$	80	11, 49
		l-Menthol and Al mentholate	75	11
		i-C_5H_{11}	53	49
α-Bromocinnamaldehyde	α-Bromocinnamyl alcohol	CME	—	8
α-Chlorocinnamaldehyde	α-Chlorocinnamyl alcohol	CME	—	8
2-, 3-, or 4-Nitrocinnamaldehyde	2-, 3-, or 4-Nitrocinnamyl alcohol	CME	70 (3-Nitro)	8
2,5,5,9-Tetramethyl-5,6,7,8,9,10-hexahydronaphthaldehyde	2,5,5,9,-Tetramethyl-5,6,7,8,9,10-hexahydronaphthyl alcohol	*i*-C_3H_7	—	50
		Heterocyclic		
Furfural	Furfuryl alcohol	C_2H_5	88	1
Oxindol-3-al	No oxindol-3-ol	C_2H_5	0	51
		i-C_3H_7	0	51

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* Unless otherwise indicated, the alkyl radical represents R of $Al(OR)_3$ in ROH. CME stands for chloromagnesium ethoxide in ethyl alcohol.

TABLE III

Reduction of Ketones

Compound reduced	Product formed	Reagent*	Per cent yield	Ref. No.
	Aliphatic			
3-Pentanone	3-Pentanol	i-C_3H_7	60	52
4-Heptanone	4-Heptanol	i-C_3H_7	92	7
4-Methyl-2-pentanone	4-Methyl-2-pentanol	i-C_3H_7	—	7
2-Undecanone	2-Undecanol	i-C_3H_7	—	53
		i-C_3H_7ONa	92	53
Mesityl oxide	4-Methyl-3-penten-2-ol	i-C_3H_7	—	54
		s-C_4H_9	25	55
cis-3-Hepten-2-one	3-Hepten-2-ol	i-C_3H_7	29	56
trans-3-Hepten-2-one	Same isomer	i-C_3H_7	—	56
2,20-Docosadiyn-12-ol-11-one 2,20-Docosadiyne-11,12-dione	α-2,20-Docosadiyne-11,12-diol	i-C_3H_7	34	57
	β-2,20-Docosadiyne-11,12-diol		46	57
Phenylacetone	1-Phenyl-2-propanol	i-C_3H_7ONa	—	53
1,1,1-Trichloroacetone	1,1,1-Trichloro-2-propanol	C_2H_5	67	1
1,1,1,3-Tetrachloroacetone	1,1,1,3-Tetrachloro-2-propanol	CME	—	8
1,1,3,3-Tetrachloroacetone	1,1,3,3-Tetrachloro-2-propanol	CME	—	8
	Alicyclic			
Cyclopentanone	Cyclopentanol	i-C_3H_7	33	7
Cyclohexanone	Cyclohexanol	i-C_3H_7	95	7
Methylcyclohexanones	Methylcyclohexanols	i-C_3H_7	90–95	7
2-Acetyl-5,6,7,8-tetrahydronaphthalene	(5,6,7,8-Tetrahydro-2-naphthyl)methylcarbinol	i-C_3H_7	85	58
1-Decalone	1-Decalol	i-C_3H_7	95	7
2,3-Diphenyl-1-tetralone	2,3-Diphenyl-1-hydroxy-1,2,3,4-tetrahydronaphthalene	i-C_3H_7	93	59
1,2,3,4,7,8,9,10-Octahydro-5,6-benz-7-azulone	1,2,3,4,7,8,9,10-Octahydro-5,6-benz-7-azulol	i-C_3H_7	100	60
l-Cryptone	*trans*-*l*-Cryptol	i-C_3H_7	—	33
Camphor	Borneol and isoborneol	i-C_3H_7	100	7
		i-C_3H_7	—	61
l-Menthone	*l*-Menthol	$C_5H_{11}ONa$	—	11
	l-Menthol and neomenthol	i-C_3H_7	90	7

Alicyclic (*Continued*)				
Carvone	*d*-Carveol	i-C_3H_7	80	11, 36, 62
		n-C_4H_9	30	36
d-Pulegone	*d*-Neoisopulegol	i-C_3H_7	—	63
Ionone	Ionol	i-C_3H_7ONa	25	53
Dihydrorhodoxanthine	Zeaxanthine	i-C_3H_7	12	17
Capsanthin	Capsanthol	i-C_3H_7	23	17
Axerophthylideneacetone	Axerophthylidene isopropyl alcohol	i-C_3H_7	—	24
Lupeone	Lupeol (no isomers)	i-C_3H_7	—	64
Nor-β-boswellanedione	Nor-β-boswellanonol	i-C_3H_7	—	65
Nor-β-boswellenone	Nor-β-boswellenol	i-C_3H_7	—	65
Breienedione	Breieneonol A	i-C_3H_7	19	66
	Breieneonol B		6	66
1-Keto-2-phenyl-1,2,3,4-tetrahydrophenanthrene	1-Hydroxy-2-phenyl-1,2,3,4-tetrahydrophenanthrene	i-C_3H_7	Excellent	67
1-Keto-3-methyl-1,2,3,4-tetrahydrophenanthrene	1-Hydroxy-3-methyl-1,2,3,4-tetrahydrophenanthrene	i-C_3H_7	85	68
4-Keto-3-methyl-1,2,3,4-tetrahydrophenanthrene	4-Hydroxy-3-methyl-1,2,3,4-tetrahydrophenanthrene	i-C_3H_7	92	68
1-Keto-3-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene	1-Hydroxy-3-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene	i-C_3H_7	—	68
1-Keto-1,2,3,4-tetrahydro-2′-methyl-5,6-benzanthracene	1-Hydroxy-1,2,3,4-tetrahydro-2′-methyl-5,6-benzanthracene	i-C_3H_7	89 (crude)	68
1-Keto-10-methyl-1,2,3,4-tetrahydrotriphenylene	1-Hydroxy-10-methyl-1,2,3,4-tetrahydrotriphenylene	i-C_3H_7	—	68
Cafestrol	No reduction	i-C_3H_7	0	61
Aromatic				
Acetophenone	α-Methylbenzyl alcohol	i-C_3H_7	93	7
		s-$C_8H_{17}ONa$	—	54
3-Nitroacetophenone	3-Nitro-α-methylbenzyl alcohol	i-C_3H_7	76	7
α,α,α-Trichloroacetophenone	2,2,2-Trichloro-1-phenyl-1-ethanol	C_2H_5	69	1
α-Bromoacetophenone	2-Bromo-1-phenyl-1-ethanol	i-C_3H_7	85	7
Benzophenone	Benzhydrol	i-C_3H_7	100	7
4-Nitrobenzophenone	4-Nitrobenzhydrol	i-C_3H_7	—	7
Benzoin	Mesohydrobenzoin	i-C_3H_7	90	7
1-Acetylnaphthalene	Methyl-1-naphthylmethanol	i-C_3H_7	95	7
2-Acetylnaphthalene	Methyl-2-naphthylmethanol	i-C_3H_7	90	7
Fluorenone	Fluorenol	i-C_3H_7	89	7

TABLE III (*Continued*)

Compound reduced	Product formed	Reagent*	Per cent yield	Ref. No.
	Heterocyclic			
2-Acetylthiophene	Methyl-2-thienylmethanol	$i\text{-}C_3H_7$	47	69
Xanthone	Xanthydrol	$i\text{-}C_3H_7$	90	7
Rubijervone	Rubijervine (isomers)	$i\text{-}C_3H_7$	—	70
Isorubijervone	Rubijervine (isomers)	$i\text{-}C_3H_7$	90 (crude)	71
Yohimbone	Yohimbol (isomers)	$i\text{-}C_3H_7$	—	72
	Amino Ketones			
1,12-Bisdiethylamino-2,11-diketododecane	No reduction	—	0	29
1,12-Dipiperidino-2,11-diketododecane	No reduction	—	0	29
α-Dialkylamino-4-bromoacetophenones	2-Dialkylamino-1-(4-bromophenyl)-1-ethanols	$i\text{-}C_3H_7$	Satisfactory	32
α-Diethyl-				
α-Di-*n*-propyl-				
α-Piperidino- (as hydrochloride)				
α-Di-*n*-butyl- (as hydrobromide)			93	
3-(4-Morpholino)acetylpyridine	1-(3-Pyridyl)-2-(4-morpholino)ethanol	$i\text{-}C_3H_7$	25	73
1-Naphthyl dialkylaminomethyl ketones	2-Dialkylamino-(1-naphthyl)-1-ethanols	$i\text{-}C_3H_7$	Satisfactory	74
4-Bromo-1-naphthyl dimethyl				
diethyl				
dipropyl				
dibutyl				
dihexyl				
4-Chloro-1-naphthyl dimethyl				
diethyl				
dipropyl				
dibutyl				
dihexyl				
piperidino				
4-Fluoro-1-naphthyl diethyl				
dibutyl				
2-Methoxy-1-naphthyl diethyl				
dibutyl				
dihexyl				
4-Methoxy-1-naphthyl diethyl				
dibutyl				

Amino Ketones (*Continued*)

9-Phenanthryl dialkylaminomethyl ketones	2-Dialkylamino-(9-phenanthryl)-1-ethanols	i-C_3H_7	Good	75
9-Phenanthryl dibutyl				
diamyl				
dihexyl				
diheptyl				
dioctyl				
dinonyl				
3-Methoxy-9-phenanthryl dialkylaminomethyl ketones	2-Dialkylamino-(3-methoxy-9-phenanthryl)-1-ethanols	i-C_3H_7	Satisfactory	76
3-Methoxy-9-phenanthryl dimethyl				
diethyl				
diamyl				
dinonyl				
dl-trans-decahydroquinolino				
1,2,3,4-Tetrahydro-9-phenanthryl dialkylaminomethyl ketones	2-Dialkylamino-(1,2,3,4-tetrahydro-9-phenanthryl)-1-ethanols	i-C_3H_7	Good	77
1,2,3,4-Tetrahydro-9-phenanthryl diamyl				
diallyl				
2-Furyl aminomethyl ketones	2-Amino-(2-furyl)-1-ethanols	i-C_3H_7		78
2-Furyl piperidino			38	
morpholino			70	
4-methylpiperidino			74	
2-Benzofuryl aminomethyl ketones	2-Alkylamino-(2-benzofuryl)-1-ethanols	i-C_3H_7		79
2-Benzofuryl diethylamino			35	
dibenzylamino			84	
benzylamino			67	
5-Bromo-2-(2-piperidinoacetyl)benzofuran	5-Bromo-2-(1-hydroxy-2-piperidinoethyl)-benzofuran	i-C_3H_7	42	79
2-(3-Piperidinopropionyl)benzofuran	2-(1-Hydroxy-3-piperidinopropyl)benzofuran	i-C_3H_7	22	79
2-(3-Morpholinopropionyl)benzofuran	2-(1-Hydroxy-3-morpholinopropyl)benzofuran	i-C_3H_7	46	79

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* Unless otherwise indicated, the alkyl radical represents R of $Al(OR)_3$ in ROH. CME stands for chloromagnesium ethoxide in ethyl alcohol.

TABLE IV

Reduction of Steroids

Compound reduced	Product formed	Reagent*	Per cent yield	Ref. No.
	Saturated			
Oxidation product from pseudotigogenin diacetate	3,16,20-Allopregnanetriol	i-C_3H_7	—	80
3,11-Uranedione	3-β-Uraneol-11-one	i-C_3H_7	—	81
Heterocholestenone	7-Hydroxy-*i*-cholesterol	i-C_3H_7	—	82
24-Keto-*i*-cholesteryl methyl ether	24-Hydroxy-*i*-cholesteryl methyl ether	i-C_3H_7	20	83
4,20-Diacetoxypregnan-3-one	Pregnane-3,4,20-triol	i-C_3H_7	—	84
	Unsaturated			
Estrone	Stereoisomeric estradiols	i-C_3H_7	—	20
Estrone benzyl ether	Estradiol benzyl ether	i-C_3H_7	—	85
4-Androstene-3,17-dione	*cis*- and *trans*-Testosterones	t-C_4H_9 in s-C_4H_9OH	70	21
Dehydroandrosterone	5-Androstene-3,17-diol	—	—	86
4-Androsten-17-ol-3-one	4-Androstene-3,17-diol	i-C_3H_7	—	87
3-Pinacol of 4-androstene-3,17-dione	3-Pinacol of 4-androsten-17-ol-3-one	i-C_3H_7	—	88
5-Pregnen-3-ol-20-one	5-Pregnene-3,20-diol	—	—	86
5-Pregnene-3,21-diol-20-one 21-monoacetate	5-Pregnene-3,20,21-triol	i-C_3H_7	—	89
4,7-Cholestadien-3-one	Stereoisomers of 4,7-cholestadien-3-ol	i-C_3H_7	—	52
3-Epiacetoxy-5-cholesten-7-one	Stereoisomers of 5-epicholestene-3,7-diol	i-C_3H_7	58	90
7-Ketocholesterol acetate	7-Hydroxycholesterol	i-C_3H_7	—	91
24-Ketocholesteryl acetate	24-Hydroxycholesteryl acetate	i-C_3H_7	94	83
Methyl 3-keto-11-etiocholenate	Stereoisomers of methyl 3-hydroxy-11-etiocholenate	i-C_3H_7	45 (α), 21 (β)	92
Zymostenone	Stereoisomers of dihydrozymosterol	i-C_3H_7	80	93
Zymostadienone	Zymosterol	i-C_3H_7	40	93
4-Dehydrotigogenone	Epi-4-dehydrotigogenin	i-C_3H_7	22	94
7-Ketoclionasteryl acetate	Isolated as 7-hydroxyclionasteryl dibenzoate	i-C_3H_7	30	95

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* Unless otherwise indicated, the alkyl radical represents R of $Al(OR)_3$ in ROH.

III. OPPENAUER OXIDATION OF HYDROXYL COMPOUNDS

1. General Considerations

The Oppenauer method for the oxidation of hydroxyl groups has proved especially valuable in work with hydroxy steroids. This procedure has been used in the study of derivatives of vitamins A and D which also require a selective oxidizing agent because of the presence of C—C double bonds and the costliness of the starting materials.

Adkins and Franklin[96] have carried out an extensive investigation of experimental conditions for the oxidation of alcohols with ketones in the presence of aluminum *tert*-butoxide. Five ketones, acetone, methyl ethyl ketone, cyclohexanone, benzil, and *p*-benzoquinone, showed special merit. Although the first three ketones readily undergo a mesityl oxide condensation, acetone and methyl ethyl ketone are valuable because of their accessibility and ease of separation from the reaction product, and cyclohexanone is useful because of its high oxidation potential and rapid action. Similarly, the high oxidation potential and rapid action of quinone may outweigh its tendency to condense and the fact that quinone and hydroquinone may interfere in the isolation of the product.

Certain of these ketones have proved advantageous in specific oxidations. Although benzil reacts slowly and is difficultly separable, it is a good oxidizing agent for the preparation of ketones or aldehydes which can be distilled from the reaction mixture below 100°C. Both benzil and quinone may be used in preparing ketones boiling from 100° to 200°C., especially if they are likely to condense. Methyl ethyl ketone and cyclohexanone are especially suited for the oxidation of high molecular weight compounds such as the steroids.

Although 0.5 mole of alkoxide per mole of alcohol to be oxidized gave good results, these investigators recommend a ratio of 1:1 in order to remove the water formed. Oppenauer[2] states that the equilibrium is displaced in favor of the dehydrogenation of the alcohol component in the presence of an excess of the oxidizing ketone. In accord with this, Adkins and Franklin[96] found that for oxidizing simple alcohols, the optimum ratios of oxidizing ketone to alcohol are 20 moles of acetone or methyl ethyl ketone, 3 to 10 moles of cyclohexanone, and 1 to 3 moles of quinone or benzil

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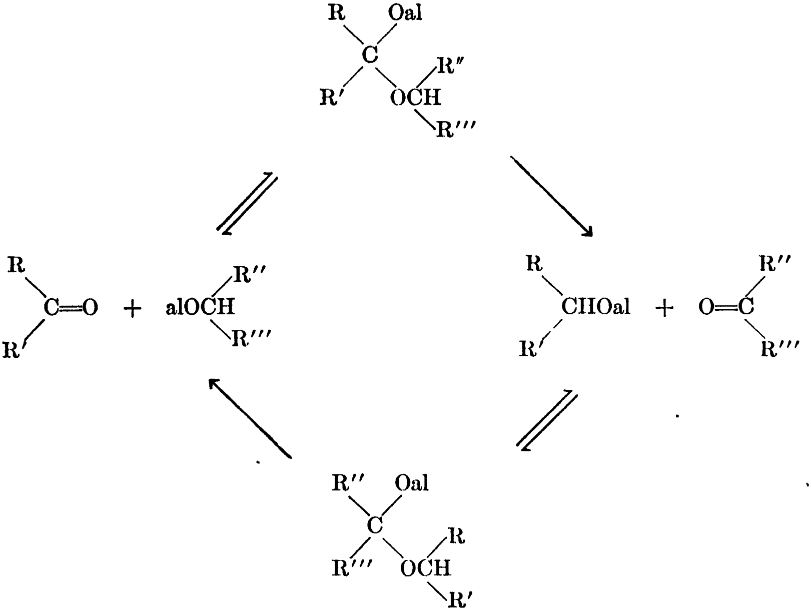
(*Footnotes to tables, concluded*)

[89] Ehrenstein, *J. Org. Chem.*, **8**, 83 (1943).
[90] Windaus and Naggatz, *Ann.*, **542**, 204 (1939).
[91] Ruzicka, Prelog, and Tagmann, *Helv. Chim. Acta*, **27**, 1149 (1944).
[92] Lardon and Reichstein, *Helv. Chim. Acta*, **26**, 607 (1943).
[93] Wieland and Benend, *Ber.*, **75**, 1708 (1942).
[94] Marker and Turner, *J. Am. Chem. Soc.*, **63**, 767 (1941).
[95] Bergmann, Lyon, and McLean, *J. Org. Chem.*, **9**, 290 (1944).
[96] Adkins and Franklin, *J. Am. Chem. Soc.*, **63**, 2381 (1941).



per mole of alcohol. The optimum ratio is 40 to 80 moles of ketone per mole of hydroxy steroid.

Benzene, toluene, and dioxane are equally good as inert solvents for diluting the reaction mixture in order to reduce the extent of condensation.[96] In certain cases a solvent is essential. For example, although the aluminum compound of cholesterol is not oxidized by acetone alone, a reaction occurs on the addition of benzene. Oppenauer[2] ascribes this phenomenon to the relative insolubility or to the slight decomposition tendency of the intermediate complex.

The Oppenauer oxidation may be carried out either at room temperature or at higher temperatures[96,97] (55° to 60°C.).[96]

Ketones are used exclusively as oxidizing agents in actual practice, although Verley[98] has demonstrated that it is possible to carry out this type of oxidation by means of aldehydes. In this work butyraldehyde and aluminum ethoxide were used for the oxidation of geraniol, but since the butyl alcohol formed was not removed and since the transformation did not occur unless benzene was present, an abnormal Tishchenko ester condensation actually occurred. Ponndorf[11] carried out an oxidation of *l*-menthol to menthone by means of cinnamaldehyde in the presence of aluminum isopropoxide. He showed also that the oxidation exchange can take place

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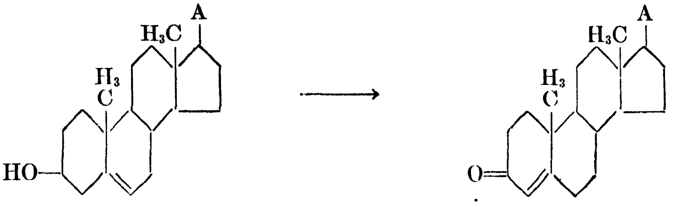
[97] Reichstein and von Euw, *Helv. Chim. Acta,* **23,** 136 (1940).
[98] Verley, *Bull. soc. chim.,* **37,** 537 (1925).

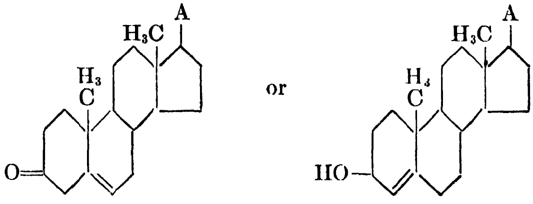
without a catalyst, although in poor yield, in a conversion of benzyl alcohol to benzaldehyde by means of anisaldehyde.

But in investigating the application of this procedure to new compounds, probably acetone (freshly distilled over calcium chloride) or cyclohexanone would be used as oxidizing agent with either aluminum *tert*-butoxide or aluminum phenoxide[99] as catalyst.

In almost all the examples published in recent years, the Oppenauer oxidation is applied to the preparation of steroid ketones according to the following general scheme:



Substituent A represents a wide variety of different side chains including ester groups, unsaturated hydrocarbon residues, acetals, etc. The migration of the C—C double bond from the 5,6 position into conjugation with the carbonyl group is usually characteristic of these transformations. The intermediate product which is postulated as:



has not yet been isolated. The Oppenauer dehydrogenation of either α,β or β,γ unsaturated alcohols yields in general α,β unsaturated ketones.[100] A preferential oxidation of the C_3 hydroxyl group of the bile acid esters has been observed.[101]

Steroid ketones themselves may also function as oxidizing agents. In certain cases dismutation occurs as well, as in Oppenauer's[2] transformation of dehydroandrosterone into testosterone.

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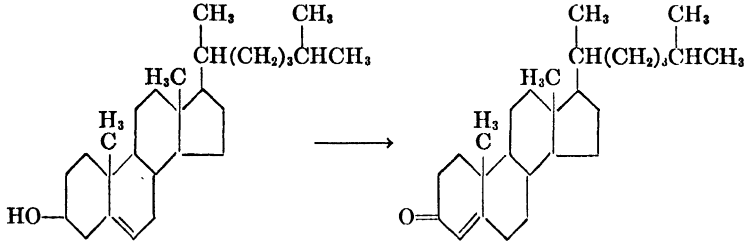
[99] Kuwata and Toyama, *J. Pharm. Soc. Japan*, **57**, 914 (1937); *Chem. Abstracts*, **32**, 1709 (1938); *Chem. Zentr.*, **1938, II**, 1612.

[100] Windaus and Roosen-Runge, *Z. physiol. Chem.*, **260**, 181 (1939).

[101] Gallagher, *J. Biol. Chem.*, **133**, xxxvi (1940).

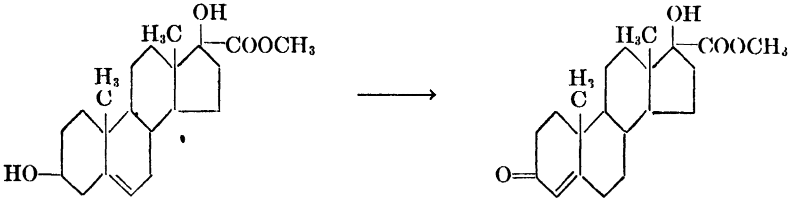
2. Examples of This Oxidation

The Oppenauer reaction has been used most extensively in the oxidation of steroids. When aluminum *tert*-butoxide and acetone are used, with benzene as the solvent, cholesterol is oxidized smoothly to cholestenone[2,102] (Eq. 1). According to a patent assigned to Schering,[103] the use of chloromagnesium ethoxide and acetone is also very satisfactory for this oxidation.

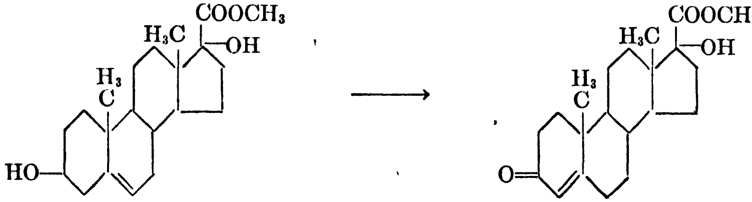


(1)

With aluminum *tert*-butoxide and acetone, methyl 3(β)17(α)-dihydroxy-5-etiocholenate is transformed into methyl 3-keto-17(α)-hydroxy-4-etiocholenate[104] (Eq. 2) and methyl 3(β),17(β)-dihydroxy-5-etiocholenate into methyl 3-keto-17(β)-hydroxy-4-etiocholenate[104] (Eq. 3). Reich and Reichstein[105] have carried out the oxidation of the dimethyl acetal of 5-pregnen-3-ol-20-on-21-al to the dimethyl acetal of 4-pregnene-3,20-dion-21-al in the same way (Eq. 4).



(2)



(3)

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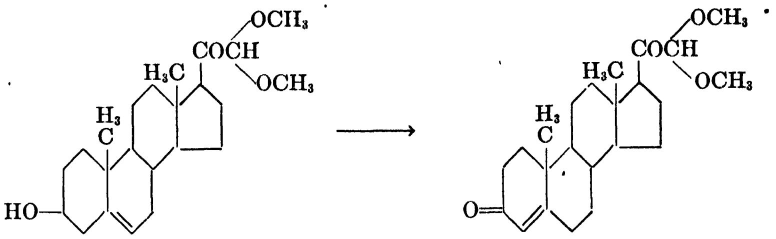
[102] See also Oppenauer, *Org. Syntheses*, **21**, 18 (1941).

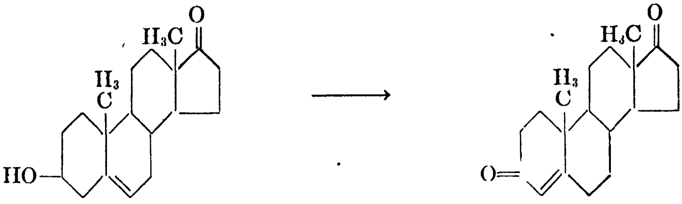
[103] Schering, French Patent, 822,551, January 4, 1938; *Chem. Zentr.*, **1938, II**, 120; *Chem. Abstracts*, **32**, 4174 (1938).

[104] Reichstein, Meystre, and von Euw, *Helv. Chim. Acta*, **22**, 1107 (1939).

[105] Reich and Reichstein, *Helv. Chim. Acta*, **22**, 1124 (1939).


(4)

Oppenauer[2] has described the preparation of 4-androstene-3,17-dione from dehydroandrosterone by means of aluminum *tert*-butoxide and acetone[86] (Eq. 5). In the partial oxidation of 5-androstene-3,17-diol to testosterone, Kuwata and Toyama[99] obtained better results with aluminum butoxide than with either aluminum ethoxide or aluminum isopropoxide and benzene (Eq. 6). The most satisfactory catalyst for this transformation is the easily prepared aluminum phenoxide, yielding 40% of testosterone.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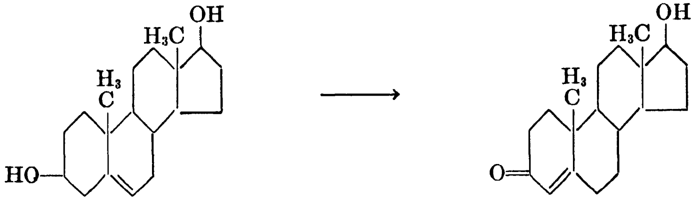
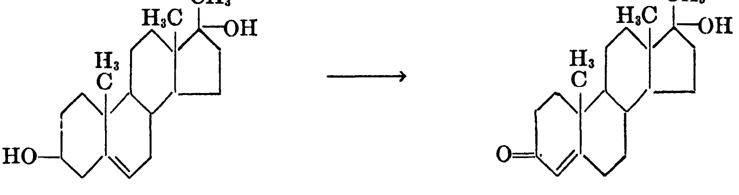

(6)

Oppenauer[2,106] described the oxidation of 17-methyl-5-androstene-3,17-diol to 17-methyltestosterone (Eq. 7), as well as the preparation of


(7)

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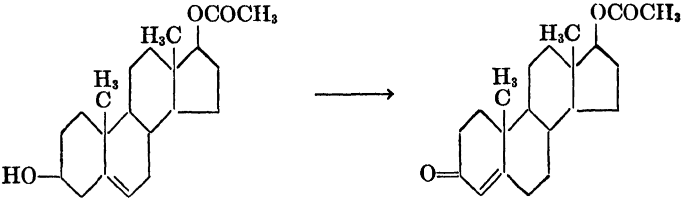
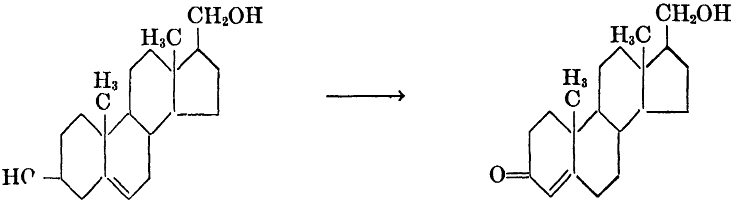
[106] See the preparation of 17-isomethyltestosterone by Miescher and Klarer, *Helv. Chim. Acta*, **22**, 962 (1939). Chinaeva, Ushakov, and Marchevskiĭ, *J. Gen. Chem.* (*U. S. S. R.*), **9**, 1865 (1939) [*Chem. Zentr.*, **1940**, **I**, 2954; *Chem. Abstracts* **34**, 4073 (1940)], have prepared 17-methyltestosterone through the oxidation of 17-methyl-3,17-androstenediol by means of acetone and aluminum isopropoxide.

testosterone acetate from 17-acetyl-5-androstene-3,17-diol, by means of aluminum butoxide (Eq. 8).



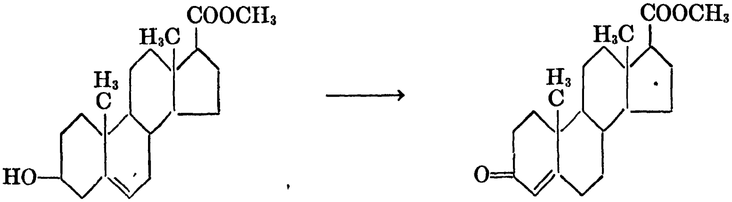
(8)

Miescher and Wettstein[107] have reported that the dehydrogenation of 17-hydroxymethyl-5-androsten-3-ol to 17-hydroxymethyl-4-androsten-3-one occurs with surprising ease through the action of aluminum isopropoxide and cyclohexanone in toluene solution (Eq. 9). These investigators have



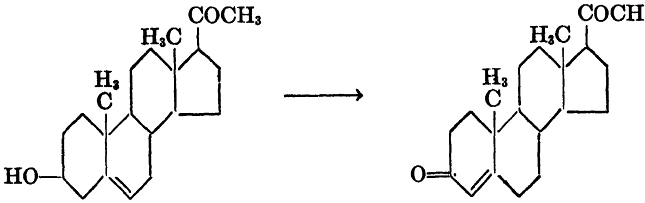
(9)

carried out the oxidation of methyl 3-hydroxy-5-etiocholenate to methyl 3-keto-4-etiocholenate by a similar procedure (Eq. 10).



(10)

The preparation of progesterone from 5-pregnen-3-ol-20-one (Eq. 11) which was reported by Oppenauer[2] and Goldberg and Aeschbacher[108] does not involve any new modifications in technique nor does the oxidation of



(11)

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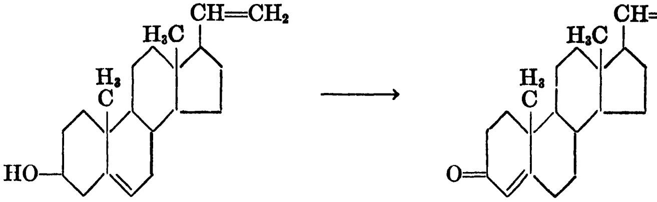
[107] Miescher and Wettstein, *Helv. Chim. Acta*, **22**, 1262 (1939).

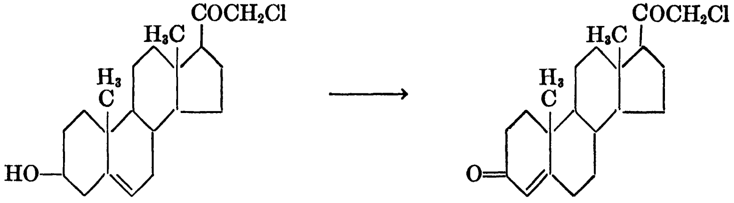
[108] Goldberg and Aeschbacher, *Helv. Chim. Acta*, **22**, 1185 (1939); see the preparation of neoprogesterone by Miescher and Kägi, *ibid.*, **22**, 184 (1939).

5,20-pregnadien-3-ol to 5,20-pregnadien-3-one (Eq. 12) by means of aluminum *tert*-butoxide and acetone as it was carried out by Ruzicka, Goldberg, and Hardegger.[109]



(12)

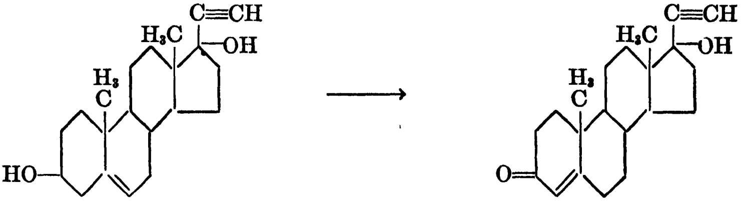
Halogenated compounds can be safely subjected to oxidation or reduction in the presence of aluminum alkoxides. This was affirmed by Reich and Reichstein[105] in a successful oxidation of 21-chloro-5-pregnen-3-ol-20-one to 21-chloroprogesterone (Eq. 13); nor was the halogen attacked in the oxidation of the corresponding bromo derivative. Fernholz and



(13)

Stavely's[110] oxidation of 22,23-dibromostigmasterol to 22,23-dibromostigmastadienone by means of aluminum butoxide and acetone in benzene may be cited in this same connection. These investigators also described the preparation of stigmastadienone from stigmasterol by aluminum isopropoxide and cyclohexanone in toluene.

The oxidation of a steroid containing an acetylenic linkage in the side chain, 17-ethinyl-5-androstene-3,17-diol forming 17-ethinyl-4-androsten-17-ol-3-one, is described in a patent assigned to Ciba[111] (Eq. 14).



(14)

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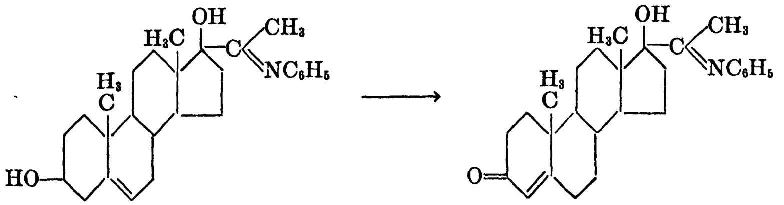
[109] Ruzicka, Goldberg, and Hardegger, *Helv. Chim. Acta*, **22**, 1294 (1939).

[110] Fernholz and Stavely, *J. Am. Chem. Soc.*, **61**, 2956 (1939).

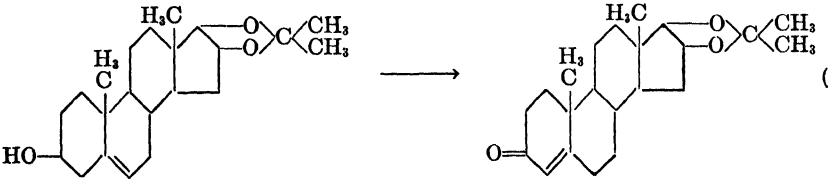
[111] Ciba, French Patent, 840,854 May 3, 1939; *Chem. Zentr.*, **1940, I**, 915; *Chem. Abstracts*, **34**, 1821 (1940). For another oxidation of 17-ethinyl-5-androstene-3,17-diol see Inhoffen, Logemann, Hohlweg, and Serini, *Ber.*, **71**, 1024 (1938).

Nitrogen-containing derivatives of the steroid series have also been subjected to the Oppenauer oxidation. Goldberg and Aeschbacher[112] report the dehydrogenation of 3,17-dihydroxy-5-pregnen-20-one anil to 3-keto-17-hydroxy-4-pregnen-20-one anil (Eq. 15).



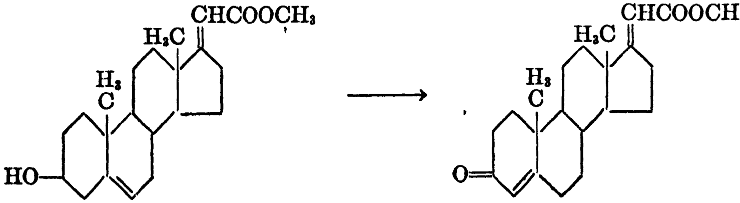
(15)

The oxidation of the corresponding acetone compound was carried out by Butenandt, Schmidt-Thomé, and Weiss[113] by means of aluminum isopropoxide and cyclohexanone in the preparation of 16-hydroxytestosterone (Eq. 16). The desired testosterone derivative was obtained after cleavage of the acetone residue.



(16)

Plattner and Schreck[114] selected aluminum *tert*-butoxide and acetone in benzene for the oxidation of methyl 3-hydroxy-5,17^{20}-pregnadiene-21-carboxylate to methyl-4,17^{20}-pregnadien-3-one-21-carboxylate (Eq. 17), as well as for the preparation of methyl 4-pregnen-3-one-21-carboxylate from methyl 3-hydroxy-5-pregnene-21-carboxylate (Eq. 18).



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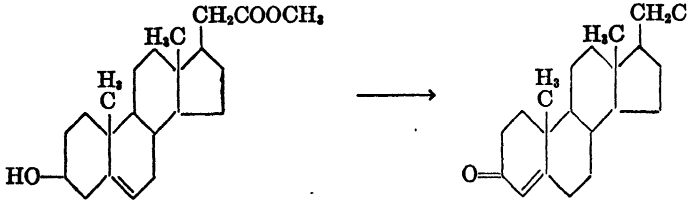

(18)

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[112] Goldberg and Aeschbacher, *Helv. Chim. Acta*, **22**, 1188 (1939).

[113] Butenandt, Schmidt-Thomé, and Weiss, *Ber.*, **72**, 417 (1939).

[114] Plattner and Schreck, *Helv. Chim. Acta*, **22**, 1178 (1939).

Two additional reactions carried out with the aluminum *tert*-butoxide-acetone combination are Oppenauer's[2] oxidation of ergosterol to ergostatrienone and the preparation of 4,7-cholestadien-3-one from 5,7-cholestadien-3-ol reported by Windaus and Kaufmann.[52]

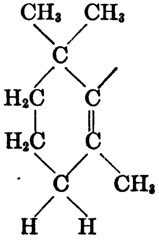
The Oppenauer reaction is relatively rarely used for the oxidation of compounds other than those of the steroid series. There is unquestionably a wide field for investigation, even though the possibility of troublesome side reactions such as condensation with the ketone compound used for dehydrogenation must be taken into consideration.[24]

Since a condensation product, axerophthylideneacetone, rather than the desired vitamin A aldehyde (axerophthal), was formed by the Oppenauer oxidation of vitamin A (Eq. 19):

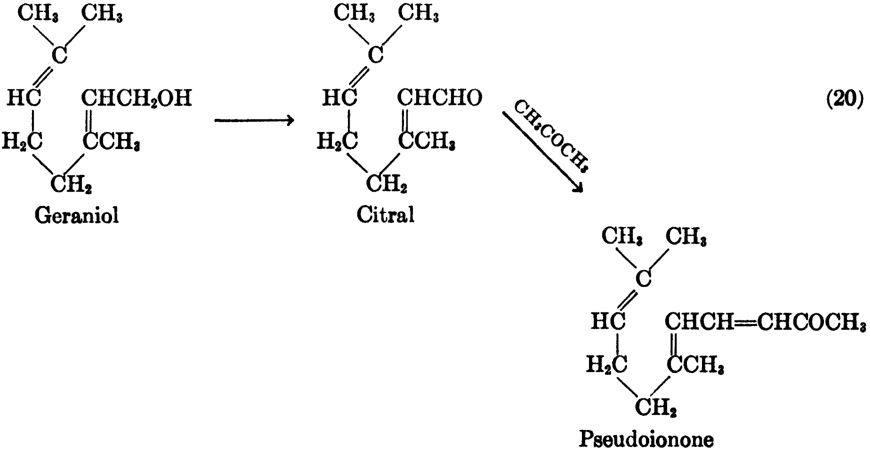
$$\mathrm{R[CH{=}CHC(CH_3){=}CH]_2CH_2OH} \longrightarrow \mathrm{R[CH{=}CHC(CH_3){=}CH]_2CHO}$$

$$\xrightarrow{+\mathrm{CH_3COCH_3}} \mathrm{R[CH{=}CHC(CH_3){=}CH]_2CH{=}CHCOCH_3} \quad (19)$$

where R =



Batty *et al.*[115] examined the course of the Oppenauer oxidation of other primary alcohols. Both citral and geraniol gave pseudoionone (Eq. 20):



(20)

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[115] Batty, Burawoy, Harper, Heilbron, and Jones, *J. Chem. Soc.*, 1938, 175.

in about 70% yield with aluminum *tert*-butoxide in the presence of acetone. Under similar conditions cinnamyl, furfuryl, and benzyl alcohols yielded respectively cinnamylidene-, furfurylidene-, and benzylideneacetones. Since tetrahydrogeraniol, 2-phenylethanol and 3-phenylpropanol were completely unreactive toward the reagents, these investigators concluded that an activating center such as an α,β double bond or an aromatic nucleus contiguous to the —CH_2OH group is necessary for the Oppenauer oxidation to take place.

Haworth *et al.*[116] oxidized vitamin A in the presence of ketones such as diethyl ketone, diisopropyl ketone, *p*-benzoquinone, and cyclohexanone, with which condensation is less probable. With diethyl ketone, the only satisfactory oxidizing agent, vitamin A aldehyde was first formed but this aldehyde was further oxidized, establishing an additional double bond in the ring. When cinnamyl alcohol was oxidized with aluminum *tert*-butoxide and diethyl ketone, cinnamylidene diethyl ketone was obtained in 35% yield; in the presence of diisopropyl ketone, 5% of cinnamaldehyde was formed.

Recently Hawkins and Hunter[117] have successfully oxidized vitamin A to the corresponding aldehyde with aluminum isopropoxide and acetaldehyde.

Windaus and Roosen-Runge[100] described the dehydrogenation of dihydrovitamin D_2 by aluminum isobutoxide and acetone in benzene. The α,β-unsaturated ketone obtained was isolated from the reaction mixture in the form of its semicarbazone.

3. Examples of Experimental Procedures

A. Cholesterol to Cholestenone

A solution of 10 g. of cholesterol in 120 g. of hot acetone is added to a solution of 12 g. of crystalline aluminum *tert*-butoxide in 300 ml. of benzene and the mixture is refluxed for 10 hours. The reaction mixture is then shaken thoroughly with dilute sulfuric acid to remove the aluminum compounds and the benzene layer is washed, dried, and concentrated. The yield of ketone, melting at 79° to 80°C. is 8.9 g. (89%).[2]

B. Methyl 3(β),17(α)-dihydroxy-5-etiocholenate to Methyl 3-keto-17(α)-hydroxy-4-etiocholenate

50 mg. of methyl 3(β),17(α)-dihydroxy-5-etiocholenate are dissolved in toluene and concentrated *in vacuo* in order to remove completely the water of hydration. The residue is refluxed, protected from moisture, for 24 hours in a ground joint flask with 4.5 ml. of dry benzene, 1.5 ml. of

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[116] Haworth, Heilbron, Jones, Morrison, and Polya, *J. Chem. Soc.*, **1939**, 128.
[117] Hawkins and Hunter, *J. Chem. Soc.*, **1944**, 411.

acetone, and 200 mg. of aluminum *tert*-butoxide which has been freshly distilled under a high vacuum. After concentrating the reaction mixture *in vacuo*, the residue is taken up in ether and dilute hydrochloric acid. The etheral solution is washed with hydrochloric acid, sodium hydroxide containing ice, and finally with water. After evaporation of the ether, the residue is treated with Girard's Reagent T in methanol-acetic acid and worked up in the usual manner.[104]

C. Dimethyl Acetal of 5-Pregnen-3-ol-20-on-21-al to Dimethyl Acetal of 4-Pregnene-3,20-dion-21-al

The dimethyl acetal of 5-pregnen-3-ol-20-on-21-al is oxidized under conditions similar to those described in the preparation above. Since an acid-sensitive group is present, certain modifications must be made in working up the reaction mixture. Reich and Reichstein[105] have used the following procedure. After evaporation of the acetone *in vacuo*, the residue is rinsed into a separatory funnel with ether and is shaken with two portions of a concentrated solution of Rochelle salt (sodium potassium tartrate) containing some sodium carbonate, with a solution of sodium carbonate, and finally with water. After evaporation of the ether, the residue is dissolved in benzene mixed with 9 parts of pentane and chromatographed over 6 g. of aluminum oxide. The oxidation and chromatographic analysis must be carried through three times in this preparation.

D. 17-Ethinyl-5-androstene-3,17-diol to 17-Ethinyl-4-androsten-17-ol-3-one

To 0.5 g. of 17-ethinyl-5-androstene-3,17-diol dissolved in 10 g. of dry acetone are added 1 g. of aluminum *tert*-butoxide and 40 g. of dry toluene. The mixture is refluxed for 21 hours, diluted with 100 g. of ether, washed with dilute mineral acid and water, and dried. After evaporation of the solvent, the 17-ethinyl-4-androsten-17-ol-3-one is distilled.[111]

(Table V follows)

TABLE V

Oppenauer Oxidations

Unless otherwise indicated in this table, the aluminum alkoxide is aluminum *tert*-butoxide. I. and P. represent aluminum isopropoxide and phenoxide, respectively. A. represents acetone, C. cyclohexanone, and Q. *p*-benzoquinone, the commonly used oxidizing ketones. If inert solvents are reported, they are indicated by B. benzene, T. toluene, X. xylene, and D. dioxane.

Compound oxidized	Product formed	Reagent*	Per cent yield	Ref. No.
	Aliphatic and Aromatic			
Phytol	6,10,14,18-Tetramethyl-3,5-nonadecadien-2-one	A.,B.	46 (crude)	118
Diphenylcarbinol	Benzophenone	Benzil, T.	83	96
		Q.	88	96
		C.	90	96
		$C_6H_5COCH_2CH(CH_3)_2$	68	96
		C_6H_5CHO	91	96
	Alicyclic			
2-Ethylcyclohexanol	2-Ethylcyclohexanone	Q.	76	96
Vitamin A alcohol	Vitamin A aldehyde (axerophthal)	I., CH_3CHO in B.	—	117
$\Delta^{9,10}$1-Octalol	$\Delta^{8,9}$1-Octalone	—	73	119
$\Delta^{9,10}$1,5-Octalindiol	$\Delta^{9,10}$1,5-Octalindione	—	30	119
cis- and *trans*-α-Decalols	α-Decalones	I.	Satisfactory	120
cis-syn-cis-Perhydro-9-phenanthrol	*trans-syn-cis*-Perhydro-9-phenanthrone	A.,B.	—	121
1-Keto-2,13-dimethyl-Δ^{9-14}-dodecahydro-7-phenanthrol	1,7-Diketo-2,13-dimethyl-Δ^{9-14}-dodecahydrophenanthrene	I.,C.,T.	—	122
1,7-Dihydroxy-1,2,13-trimethyl-Δ^{9-14}-dodecahydrophenanthrene	7-Keto-1,2,13-trimethyl-Δ^{8}-dodecahydro-1-phenanthrol	I.,C.,T.	—	122
1,7-Dihydroxy-2,13-dimethyl-1-ethinyl-Δ^{9-14}-dodecahydrophenanthrene	7-Keto-2,13-dimethyl-1-ethinyl-Δ^{8}-dodecahydro-1-phenanthrol	I.,C.,T.	—	122
Betulin	Betulonaldehyde	Q.,B.	33	123
Lupeol	Lupeone	Q.	—	64

		Heterocyclic		
Rubijervine	Rubijervone	A.,B.	55 (crude)	71
Isorubijervine	Isorubijervone	A.,B.	55	71
Yohimbine	Yohimbone	P.,C.,X.	90	124
Alloyohimbine	Alloyohimbone	P.,C.,X.	—	124
Yohimboaic acid	Yohimbone	P.,C.,X.	—	124
Alloyohimboaic acid	Alloyohimbone	P.,C.,X.	—	124
Yohimbenic acid	Yohimbenone	P.,C.,X.	—	124
3-Solanidanol	3-Solanidanone	P.,A.,B.	—	125
Solanidine	Δ^4-Solanidenone	A.,B.	91	125
		Saturated Steroids		
3,5-Androstanediol-17-one	4-Androstene-3,17-dione	A.,B.,D.	—	126
3,11-Androstanediol-17-one	11-Androstanol-3,17-dione	P.,A.,B.	—	127
17-Hexahydrobenzoate of 3,17-androstanediol	17-Hexahydrobenzoate of 17-androstanol-3-one	Q.,T.	—	128
3,11-Uranediol	11-Uraneol-3-one	I.,C.,T.	—	81
Sterol B	A ketone	A.	Small	129
3,5,6-Clionastanetriol	5-Clionastenol-3,6-dione	I.,A.,B.	—	130
3,17,20-Allopregnanetriol	17,20-Allopregnanediol-3-one	P.,A.,B.	—	127
3,16,20-Pregnanetriol	17-Pregnene-3,16-dione	I.,C.,T.	—	131
3,16,20-Allopregnanetriol	16-Allopregnene-3,20-dione	I.,C.,T.	47	131
12-Acetoxypregnane-3,7-diol-20-one	12-Acetoxypregnan-7-ol-3,20-dione	I.	47 (crude)	132
3-Acetoxypregnane-3,11,20-triol	3-Acetoxypregnane-3,11-diol-20-one	P.,A.,B.	16–21	133
21-Acetoxypregnane-3,11,21-triol-20-one	21-Acetoxypregnane-11,21-diol-3,20-dione	P.,A.,B.	42	134
21-Acetoxypregnane-3,12,21-triol-20-one	21-Acetoxypregnane-12,21-diol-3,20-dione	P.,A.,B.	41	135
20-Methylpregnane-3,16,20-triol	20-Methyl-17,20-pregnene-3,16-dione		—	136
Methyl etiodesoxycholate	Methyl 3-keto-12-hydroxyetiocholanate	C.,T.	37	137
Methyl bisnordesoxycholate	Methyl 3-keto-12-hydroxybisnorcholanate	C.,T.	78	137
Methyl nordesoxycholate	Methyl 3-keto-12-hydroxynorcholanate	C.,T.	65	137
Methyl desoxycholate	Methyl 3-keto-12-hydroxycholanate	C.,T.	63	137

TABLE V (*Continued*)

Compound oxidized	Product formed	Reagent	Per cent yield	Ref. No.
	Unsaturated Steroids			
Diacetate of 5-androstene-3,17-diol	No reduction	Q.,T.	0	128
17-Methyl-3,17-androstenediol	17-Methyltestosterone	I.,A.,B.	41	138,139
17-Allylandrostene-3,17-diol	17-Allyltestosterone	A.,B.	70	140
17-Acetonyliden-5-androsten-3-ol	17-Acetonyliden-4-androsten-3-one	A.,B.	76	141
17-Acetonyl-5-androsten-3-ol	17-Acetonyl-4-androsten-3-one	A.,B.	83	141
17*a*-Methyl-D-homo-5,17-androstadien-3-ol	17*a*-Methyl-D-homo-4,17-androstadien-3-one	A.,B.	74 (crude)	142
17*a*-Methyl-D-homo-5-androstene-3,17*a*-diol-17-one	17*a*-Methyl-D-homo-4-androsten-17*a*-ol-3,17-dione	—	—	143
10-Norpregnen-3-ol-20-one	10-Norprogesterone	A.	35	144
5-Pregnene-3,17-diol-20-one	A diketone	I.,C.,T.	34	145
	17*a*-Methyl-D-homo-5-androstene-3,17*a*-diol-17-one	A.,B.	80 (crude)	146
	17*a*-Methyl-D-homo-4-androsten-17*a*-ol-3,17-dione	A.,B.	—	147
17-Hydroxyprogesterone	17*a*-Methyl-D-homo-4-androsten-17*a*-ol-3,17-dione	A.,B.	30	148
Dimethyl acetal of 5-pregnene-3,20-diol-21-al 20-monoacetate	Dimethyl acetal of 4-pregnen-20-ol-3-one-21-al 20-monoacetate	A.,T.	67	149
Dimethyl acetal of 5-pregnene-3,20-diol-21-al	Dimethyl acetal of 4-pregnen-20-ol-3-one-21-al	A.,B.	60	149
		I.,C.,T.	51	149
20,21-Monoacetone-5-pregnene-3,17,-20,21-tetrol	20,21-Monoacetone-4-pregnene-17,20,-21-triol-3-one	A.,B.	55–58	150
5,20-Pregnadien-3-ol	4,20-Pregnadien-3-one	A.,B.	88	109
17-Acetate of 5,20-pregnadiene-3,17-diol	17-Acetate of 4,20-pregnadien-17-ol-3-one	A.,B.	29	151
21-Bromopregnenolone	21-Bromoprogesterone	—	—	104
21-Chloropregnenolone	21-Chloroprogesterone	—	—	104
21-Chloro-5-pregnen-3-ol-20-one	21-Chloroprogesterone	A.,B.	72	97
21-Diazo-5-pregnen-3-ol-20-one	21-Diazoprogesterone	A.,B.	—	97
21-Diazo-10-norpregnen-3-ol-20-one	21-Diazo-10-norprogesterone	A.	100	144
Diethylmercaptal of 5-pregnen-3-ol-20-one-21-al	Diethylmercaptal of 4-pregnene-3,20-dion-21-al	A.,B.	66	149
16-Methyl-5-pregnen-3-ol-20-one	16-Methylprogesterone	A.,T.	61	152

16-Isopropyl-5-pregnen-3-ol-20-one	16-Isopropylprogesterone	A.,T.	57	152
16-*t*-Butyl-5-pregnen-3-ol-20-one	16-*tert*-Butylprogesterone	A.,T.	63	152
21-Methyl-5-pregnen-3-ol-20-one	21-Methylprogesterone	I.,C.,T.	—	153
21-Ethyl-5-pregnen-3-ol-20-one	21-Ethylprogesterone	I.,C.,T.	—	153
21-Benzal-5-pregnen-3-ol-20-one	21-Benzalprogesterone	A.,T.	—	154
21-Benzyl-5-pregnen-3-ol-20-one	21-Benzylprogesterone	A.,T.	—	154
Cholesterol	Cholestenone	I.,C.,T.	—	155
		Methyl ethyl ketone	84	96
		A.,B.	70–86	102,156,157
		—	86	158
Epicholesterol	Cholestenone	A.,B.	—	159
4-Cholestene-3,6-diol	Cholestane-3,6-dione	I.,A.,B.	70	160
5,7-Cholestadien-3-ol	4,7-Cholestadien-3-one	A.,B.	—	52
Zymosterol	Zymostadienone	I.,A.,B.	60 (crude)	155
Dihydrozymosterol	Zymostenone	I.,C.,T.	54 (crude)	155
Neoergosterol	Corresponding ketone	I.,C.,T.	—	161
Clionasterol	Clionasterone	I.,C.,T.	—	130,162
Tall oil sitosterol	Δ^4,β-Sitostenone	A.,B.	66	158
β-Sitosterol	Sitostenone	—	15	156
Fucosterol	Fucostadienone	—	50	156
Stigmasterol	Stigmastadienone	—	58	156
Lanosterol	No reduction	A.	0	163
Diosgenin	4,6-Dehydrotigogenin	I.,Q.,T.	30	94
5-Norcholen-3-ol-22-one	4-Norcholene-3,22-dione	I.,C.,T.	—	164
3-Hydroxy-5-ternorcholenyl methyl ketone	3-Keto-4-ternorcholenyl methyl ketone	C.,T.	85 (crude)	165
3-Hydroxy-5-ternorcholenyl ethyl ketone	3-Keto-4-ternorcholenyl ethyl ketone	C.,T.	70 (crude)	165
3-Hydroxy-5-ternorcholenyl isoamyl ketone	3-Keto-4-ternorcholenyl isoamyl ketone	C.,T.	66 (crude)	165
3-Hydroxy-5-ternorcholenyl phenyl ketone	3-Keto-4-ternorcholenyl phenyl ketone	C.,T.	70	165
3-Hydroxy-20-isoternorcholenyl methyl ketone	3-Keto-20-isoternorcholenyl methyl ketone	C.,T.	90 (crude)	165
2-(3-Hydroxy-5-ternorcholenyl)propene	2-(3-Keto-4-ternorcholenyl)propene	C.,T.	66	166
2-(3-Hydroxy-20-iso-5-ternorcholenyl)-propene	2-(3-Keto-20-iso-4-ternorcholenyl)propene	C.,T.	70	166
3-Hydroxy-23-acetoxy-5-norcholen-22-one	23-Acetoxy-4-norcholene-3,22-dione	I.,C.,T.	—	164
Methyl 3-hydroxy-5-etiocholenate	Methyl 3-keto-4-etiocholenate	I.,C.,T.	—	107

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The Use of Biochemical Oxidations and Reductions for Preparative Purposes

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I. INTRODUCTION

With a knowledge of the enzymic nature of fermentation and putrefaction processes, it is possible to take advantage of the metabolic peculiarities of certain organisms for carrying out desired chemical transformations. The most extensive use of living microorganisms is made in the fermentation industries where acetic, lactic, and citric acids, alcohols,[1] and other compounds[2] such as acetone are produced by yeasts, molds, and bacteria.[3]

Under normal conditions of fermentation, these compounds are the principal end-products of the metabolism of the microorganisms concerned, but it is possible to vary the type of compounds produced by changing the conditions in such a way as to increase the production of substances which are otherwise only intermediates or formed in traces. The preparation of glycerol by yeast fermentation of hexose in the presence of sodium sulfite is an example.

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[1] Because of the recent interest in the preparation of butadiene, the formation of 2,3-butanediol in fermentation processes has undergone extensive investigation with a view to commercial production. Various carbohydrates have been employed as substrates and several bacteria have proved useful for achieving yields of approximately 80%. For a detailed description of the experimental procedure, the following articles may be consulted: Ward, Pettijohn, and Coghill, *Ind. Eng. Chem.*, **37**, 1189 (1945); Neish, Blackwood, and Ledingham, *Science*, **101**, 245 (1945); Liebmann, *Oil and Soap*, **22**, 31 (1945); U. S. Patent, 2,344,025 (National Agrol Company), March 14, 1944 [*Chem. Abstracts*, **38**, 3412 (1940)]. Other workers have been interested in the specific isomers of 2,3-butanediol produced by certain bacteria: Underkofler, Fulmer, and Kooi, *Iowa State Coll. J. Sci.*, **18**, 377 (1944); Ward, Pettijohn, Lockwood, and Coghill, *J. Am. Chem. Soc.*, **66**, 541 (1944); Morrell and Auernheimer, *ibid.*, **66**, 792 (1944).

[2] The preparation of itaconic acid, $CH_2{=}C(COOH)CH_2COOH$, by a fermentation process has been investigated recently. Because of the possible use of this acid in plastics, a cheaper method of production than by the pyrolysis of citric acid was desirable. Optimum conditions for the production of itaconic acid from glucose by *Aspergillus terreus* have been worked out both for laboratory and semipilot plant scale quantities; see Lockwood and Reeves, *Arch. Biochem.*, **6**, 455 (1945); Moyer and Coghill, *ibid.*, **7**, 167 (1945); Lockwood and Ward, *Ind. Eng. Chem.*, **37**, 405 (1945).

[3] For two recent review articles on fermentation processes see: Nilsson, *Naturwissenschaften*, **31**, 25 (1943); Christensen, *Iowa State Coll. J. Sci.*, **19**, 249 (1945).

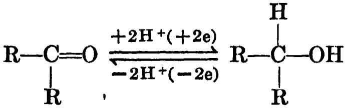
The action of microorganisms is not confined to those substances which take part in metabolism in nature, and a great variety of compounds have been found which are susceptible to biochemical transformations. Thus indigo blue may be reduced by a fermentation process, and many pharmaceuticals undergo changes in the animal organism. All such compounds probably possess certain structural similarities to the natural substrate of the enzyme systems involved.

Furthermore, it is possible, with the experience gained in the last century, to carry out a desired reaction with substances which normally take little or no part in the metabolism of certain organisms. The preparative uses of biochemical oxidations and reductions discussed in this article will be limited to this third case.

II. SURVEY OF REACTION TYPES

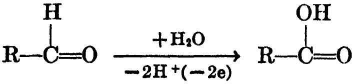
Although biological oxidations and reductions brought about by means of metabolic processes have been extensively investigated from the biological point of view, comparatively few of these transformations have been utilized for the preparation of particular compounds. The importance and potential value of these reactions warrant further investigation.

For preparative work, the best known and most easily executed transformation is the reduction of aldehydes and ketones to the corresponding alcohols, together with the reverse reaction, the dehydrogenation of primary and secondary alcohols to the corresponding carbonyl compounds. The reduction of quinones and quinoid substances and the oxidation of hydroquinones are also included in the discussion of this type of reaction.



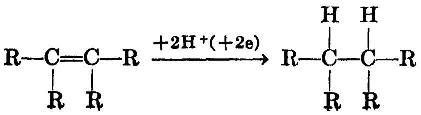
$$R{-}\underset{R}{\underset{|}{C}}{=}O \underset{-2H^+(-2e)}{\overset{+2H^+(+2e)}{\rightleftharpoons}} R{-}\overset{H}{\overset{|}{\underset{R}{\underset{|}{C}}}}{-}OH$$

The oxidation of aldehydes to acids is especially important in investigations with the sugars.



$$R{-}\overset{H}{\overset{|}{C}}{=}O \xrightarrow[-2H^+(-2e)]{+H_2O} R{-}\overset{OH}{\overset{|}{C}}{=}O$$

Up to the present time the hydrogenation of ethylenic compounds has been limited to certain classes of unsaturated substances. The reverse reaction, the formation of an ethylenic compound from a saturated ali-



$$R{-}\underset{R}{\underset{|}{C}}{=}\underset{R}{\underset{|}{C}}{-}R \xrightarrow{+2H^+(+2e)} R{-}\overset{H}{\overset{|}{\underset{R}{\underset{|}{C}}}}{-}\overset{H}{\overset{|}{\underset{R}{\underset{|}{C}}}}{-}R$$

phatic hydrocarbon derivative, has been definitely accomplished only with the pair of compounds succinic acid-fumaric acid.

The oxidation of methyl groups to carboxyl groups in aliphatic, alicyclic, and aromatic compounds takes place in the animal organism.

$$R{-}CH_3 \longrightarrow R{-}COOH$$

In addition to the general reaction types outlined above, other kinds of biological oxidation-reduction reactions are known. Examples of these are (*1*) the reversible enzymic dehydrogenation of *d*-amino acids and of *l*(+)-glutamic acid to the corresponding imino acids which are then further hydrolyzed to the keto acids[4]; (*2*) the oxidation in animal organisms of benzene[5] and pyridine[6] derivatives to phenols[7]; (*3*) the reduction of nitro, nitroso, and hydroxylamino compounds to amines through the use of yeast[8]; and finally (*4*) the hydrogenation with yeast of thioaldehydes[9] and disulfides[10] to thio alcohols.

However, most of these transformations are rarely of value in synthetic work. Other non-biochemical processes are available for these oxidations and reductions, but the use of microorganisms or enzyme preparations should still be considered in cases in which the specificity of the effects obtainable becomes important. For example, if the substrate molecule contains other sensitive groups which are to remain unchanged, and if a selected steric transformation is desired, biochemical oxidations and reductions should be investigated.

The use of fermenting yeast for the reduction of simple aldehydes has no preparative value, but has merit in the case of unsymmetrical ketones if the preparation of an optically active secondary alcohol is desired. In order to obtain exclusively α,β-reduction in conjugated polyethylenic aldehydes or ketones, biochemical hydrogenation is the only practical method.

In some of the reactions mentioned in the following discussion the biochemical process possesses no advantage over other methods, but these examples are included because of possible preparative value in other cases. It is more desirable to show the generality of the transformations than to portray interesting individual cases.

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The articles cited[11] on bacteriological, microbiological, and fermentation chemistry describe methods for the recognition and treatment of microorganisms and for obtaining enzyme preparations.

III. OXIDATION AND REDUCTION OF HYDROXYL AND CARBONYL COMPOUNDS

1. General Considerations

Biochemical reduction of the carbonyl group in numerous simple aliphatic and aromatic aldehydes has been carried out principally by fermenting yeasts (*phytochemical reduction*). However, this reaction is also brought about by bacteria, higher plants, and in animal organisms. The reverse reaction, the dehydrogenation of alcohols, takes place best through the action of bacteria. Examples are found in the use of acetic acid bacteria with ethyl alcohol and polyhydroxy alcohols, such as glycerol or sorbitol, and of *Corynebacterium*, isolated from yeast suspensions, with the sterols.

The chemistry of these reversible conversions of carbonyl and hydroxyl compounds has been well clarified, especially so far as it concerns the oxidation and reduction in carbohydrate degradation.[12] In comparison, the mechanism of dehydrogenation of higher alcohols, such as the sterols, has not yet been so well investigated. Most of the carbonyl-hydroxyl dehydrogenases have in common coenzyme I or diphosphopyridine nucleotide (cozymase) as the prosthetic group. This is true, for example, in the reactions ethyl alcohol → acetaldehyde, α-glycerophosphate → phosphoglyceraldehyde, lactic acid → pyruvic acid, malic acid → oxalacetic acid, and β-hydroxybutyric acid → acetoacetic acid.[13] Some enzymes operate with coenzyme II (triphosphopyridine nucleotide) instead of coenzyme I.

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[11] For example, Bernhauer, *Gärungschemisches Praktikum*, 2nd ed., Springer, Berlin, 1939; Glaubitz, *Atlas der Gärungsorganismen*, Berlin, 1934; Henneberg, *Handbuch der Gärungsbakteriologie*, Parey, Berlin, 1926; Janke, *Allgemeine technische Mikrobiologie: I. Die Mikroorganismen*, Dresden and Leipzig, 1924; Jørgensen, *Die Mikroorganismen der Gärungsindustrie*, 6th ed., Hansen and Lund, Jena, 1940; Kraus and Uhlenhuth, *Handbuch der mikrobiologischen Technik*, Urban & Schwarzenberg, Berlin and Vienna, 1923; Lindner, *Atlas der mikroskopischen*, *Grundlagen der Gärungskunde*, 6th ed., Parey, Berlin, 1928; Oppenheimer, *Die Fermente und ihre Wirkungen*, Thieme, Leipzig, 1926, and supplementary volumes, The Hague, 1939; Oppenheimer and Pincussen, *Die Methodik der Fermente*, Thieme, Leipzig, 1928, Vol. III of *Die Fermente und ihre Wirkungen*; Goddard, in Höber, *Physical Chemistry of Cells and Tissues*, Blakiston, Philadelphia, 1945; Green, *Mechanisms of Biological Oxidations*, Cambridge University Press, Cambridge, 1940; Kalckar, *Chem. Revs.*, 28, 71 (1941); Oppenheimer and Stern, *Biological Oxidation*, Nordeman, New York, 1939 (Interscience, N. Y.); Stephenson, *Bacterial Metabolism*, Longmans, Green, London, 1939. For a comprehensive treatment of the action of microorganisms see Fulmer and Werkman, *An Index to the Chemical Action of Microorganisms on the Non-nitrogenous Organic Compounds*, Thomas, Springfield, Ill., 1930; H. Tauber, *Enzyme Technology*, Wiley, N.Y., 1943; S. C. Prescott and C. G. Dunn, *Industrial Microbiology*, McGraw-Hill, N. Y., 1940.

[12] Since free radicals dehydrogenate aliphatic molecules, analogies between free radical chain oxidations and biochemical oxidations catalyzed by dehydrogenases are pointed out by Waters, *Trans. Faraday Soc.*, 39, 140 (1943).

The hydrogenation of a carbonyl compound (B) may take place according to Equation 2 under the influence of the specific protein of the corresponding dehydrogenase.

$$AH_2 + Co \underset{}{\overset{\text{Protein A}}{\rightleftharpoons}} A + CoH_2 \qquad (1)$$

$$B + CoH_2 \underset{}{\overset{\text{Protein B}}{\rightleftharpoons}} BH_2 + Co \qquad (2)$$

This occurs in most cases through oxidation-reduction with dihydrocoenzyme (CoH_2) whether it is in normal cell reactions or in one of the enzymic reactions carried out for preparative purposes. All the materials under consideration are hydrogen donors (AH_2) which reduce codehydrogenase through the action of a dehydrogenase either directly according to Equation 1 (for instance, hexose phosphate, triose phosphate, lactic acid, and ethyl alcohol) or indirectly via other enzyme systems. The direction in which the equilibrium reactions represented above are displaced depends upon the specific components of the system. In the case of the dehydrogenation of triose phosphates (according to Negelein and Brömel[14] 1,3-glyceraldehydediphosphoric acid) the reaction yielding hydrogen to codehydrogenase predominates. The opposing reaction, the dehydrogenation of a hydroxyl compound (BH_2), must also be taken into consideration.

In general, present knowledge[15] indicates that if these dehydrogenations proceed further, yielding water by reduction of molecular oxygen, other catalytic systems, such as the flavin enzymes and the cytochrome system, are involved. In addition to these enzymes, the four-carbon dicarboxylic acids and the tricarboxylic acid cycle (citric acid cycle) play a fundamental role in the complete oxidation of metabolic substances.[16]

It has been claimed that a few dehydrogenases contain no dissociating groups, and that in any case they employ neither of the two known codehydrogenases for their effect.[17] Thus in animal tissues, plant seeds, and yeast there may be an independent glycerophosphate dehydrogenase in addition to codehydrogenase. In contrast to the transformation of lactic acid to pyruvic acid by means of dehydrogenase from bacteria or animal tissues, the conversion using a ferment preparation from yeast often requires no addition of cozymase.

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[13] Fischer, "Niedermolekulare Überträger biologischer Oxydo-Reduktionen," *Ergeb. Enzymforsch.*, 8, 185 (1939).

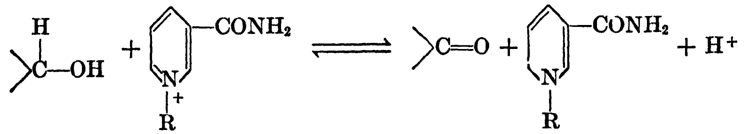
[14] Negelein and Brömel, *Biochem. Z.*, **301**, 135 (1939).

[15] See for example: Lockhart, *Biochem. J.*, **33**, 613 (1939).

[16] See for example: Martius, *Ergeb. Enzymforsch.*, **8**, 247 (1939); Krebs, in *Advances in Enzymology*, Interscience, New York, 1943, Vol. III, p. 191.

[17] Fischer, *Ergeb. Enzymforsch.*, **8**, 185 (1939).

With the exception of those few cases in which the oxidizable-reducible prosthetic group of the enzyme is still unknown, the mechanism of carbonyl-hydroxyl transformations involves a coupled oxidation-reduction in the pyridine-dihydropyridine nucleus of both oxidation stages of codehydrogenase (Eq. 3).[18] An important point to consider is the fact that the equilibrium is dependent on the pH of the reaction medium. With increasing alkalinity, the equilibrium is strongly displaced toward the formation of the carbonyl compound, while at the same time the velocity of dehydrogenation of the hydroxyl compound increases and the velocity of hydrogenation of the carbonyl compound decreases. Probably enzymic dehydrogenations of alcohols are best carried out in a weakly alkaline medium unless other factors make this procedure inadvisable.


(3)

(R represents ribose-phosphoric acid-phosphoric acid-ribose-adenine)

According to recent evidence, a flavoprotein must be present, in addition to the dehydrogenase-codehydrogenase complex, for the reduction of quinoid compounds by the enzyme systems of yeast and of animal tissues. In order to transform a quinone, such as methylene blue, into a hydroquinone, the substrate hydrogen of the hydrogenated codehydrogenase must be transferred to some extent to the isoalloxazine nucleus. This explains why most kinds of cells reduce only those quinones whose normal potential is essentially no lower than that of the flavin group, about −0.22 to 0.27 volt.[19] In metabolic processes, different bacteria can attain the reduction intensity of the hydrogen electrode, and molecular hydrogen is formed in reversible reactions.[20] At present the zymochemical reduction of quinoid substances, such as the historical example of the enzymic reduction of indigo, is of very little value for preparative purposes.

2. Zymochemical Reduction of Aldehydes and Ketones

Neuberg[21] has made an exhaustive survey of methods reported for the reduction of carbonyl compounds by fermenting yeast.[22,23] Both aliphatic and cyclic aldehydes and ketones have been subjected to phytochemical reduction. Since a comprehensive treatment of fermentation methods has been published by Neuberg and Gorr,[24] a more detailed account is omitted here. The procedure is simple: the carbonyl compound, in solution or in a fine suspension, is added to actively fermenting yeast. The fermentation requires from a day to a month for completion, with further addition during that period of sugar and of yeast, if necessary. In most cases the reaction times specified in the literature as being necessary can be materially shortened through the use of vigorous stirring. In general, aldehydes are reduced more rapidly than ketones. In order to reduce sensitive aldehydes, their ammonia or sulfite addition compounds are subjected to yeast action. Extensive systematic surveys are not yet available on the relation between reduction velocity of the added carbonyl compound and acidity of the fermenting material.

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[18] Fischer, *Ergeb. Enzymforsch.*, **8**, 190 (1939).

[19] Fischer, *Ergeb. Enzymforsch.*, **8**, 207 ff. (1939).

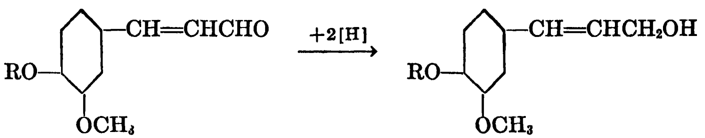
[20] Hewitt, *Oxidation-Reduction Potentials in Bacteriology and Biochemistry*, King, London, 1936.

[21] See Oppenheimer, *Die Fermente und ihre Wirkungen*, Thieme, Leipzig, 1928, Vol. II, pp. 1547 ff.

[22] Neuberg and Steenbock, *Biochem. Z.*, **52**, 494 (1913).

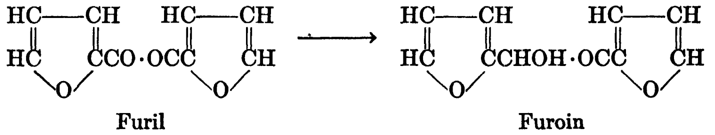
[23] Lintner and Liebig, *Z. physiol. Chem.*, **72**, 449 (1911).

Three specific examples of the application of this method to sensitive compounds may be mentioned: the reduction of tetraacetylglucoconifer-

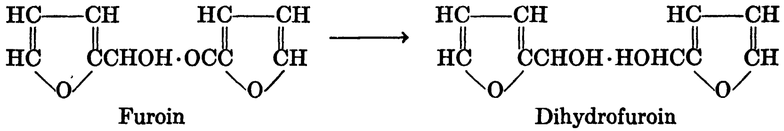


(4)

aldehyde to the corresponding alcohol[25] (Eq. 4); the hydrogenation of furil to furoin (Eq. 5); and the conversion of furoin to dihydrofuroin (Eq. 6).[26]



(5)



(6)

Bacterial reduction, which had been worked out for the simpler carbonyl compounds, has been applied in recent years to the reduction of carbonyl groups in the steroids.[27] In many cases the reduction of other ketones has been demonstrated in animal organisms,[28] but the examples described are still of little value in synthetic work.

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[24] In Oppenheimer and Pincussen, *Die Methodik der Fermente*, Thieme, Leipzig, 1928, Vol. III of *Die Fermente und ihre Wirkungen*, p. 1212. See also Bernhauer, *Gärungschemisches Praktikum*, 2nd ed., Springer, Berlin, 1939.

[25] Pauley and Feuerstein, *Ber.*, **60**, 1031 (1927).

[26] Neuberg, Lustig, and Cagan, *Arch. Biochem.*, **1**, 391 (1943).

[27] Neuberg and Simon, *Biochem. Z.*, **190**, 226 (1927).

Enzymic reduction as an important preparative method has been superseded by the smooth reduction achieved with the Meerwein-Ponndorf procedure.[29] Many unsaturated or otherwise sensitive carbonyl compounds for which only the fermentative reduction had been available may now be transformed into alcohols by means of isopropyl alcohol in the presence of aluminum isopropoxide. However, the use of the fermentation method is still unsurpassed for the preparation of specific stereoisomers.

3. Dehydrogenation of Alcohols

The feasibility of dehydrogenating mono- and polyhydroxy alcohols by bacteria, fungi, higher plant life, and in the animal organism has been demonstrated. The action of bacteria of the genus *Acetobacter*[30] is useful for the oxidation of some monohydroxy alcohols closely related to ethyl alcohol, and also for polyhydroxy sugar alcohols.

A. Monohydroxy Alcohols

The biochemical dehydrogenation of simple primary alcohols to aldehydes is rarely used in preparative work. It is difficult to stop the reaction at the aldehyde stage, since the acid forms rapidly in most cases, as in the production of vinegar by fermentation. However, the yield of aldehyde by fermentation is improved in the presence of calcium or sodium sulfite which forms a stable addition product with the aldehyde.[31]

The enzymic method is not always preferable to the oxidation-reduction exchange with ketones in the presence of aluminum alkoxides for the oxidation of unsaturated or otherwise sensitive alcohols. The applicability of the latter method using diethyl ketone and aluminum *tert*-butoxide has been established in the dehydrogenation of vitamin A to the corresponding aldehyde.[32] However, one instance where bacterial dehydrogenation of secondary hydroxyl groups to ketone groups has attained importance is in the sugar alcohols and in the sterols, and it has been carried out repeatedly with such compounds.

B. Polyhydroxy Alcohols

Since Bertrand's discovery in 1896 that his "sorbose bacterium" (*Acetobacter xylinum*) converted different polyhydroxy alcohols into the corresponding ketoses, this transformation has been accomplished by other species of *Acetobacter*. According to Bertrand, the oxidation is limited to secondary alcohol groups to which another hydroxyl group must be adjacent and in the *cis* position. For this reason xylitol and dulcitol are not attacked, but erythritol yields erythrulose[33,34]; *l*-arabitol, *l*-xyloketose; adonitol, *l*-adonose[35]; *d*-sorbitol, *l*-sorbose[36]; mannitol, *d*-fructose[33,37]; *i*-inositol, diketoinositol[38]; perseitol, perseulose[39]; α-glucoheptitol, *l*-glucoheptulose[40]; and meso-2,3-butanediol yields acetylmethylcarbinol.[41] Since gluconic acid can be dehydrogenated to 2-ketogluconic acid in addition to *d*-5-keto gluconic acid, it is obvious that an adjacent carboxyl group has the same activating effect.[42]

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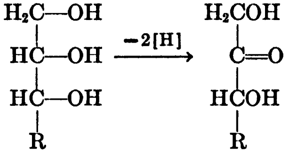
[28] Fromherz, *Bethes Handbuch der normalen und pathologischen Physiologie*, Springer, Berlin, 1929, Vol. V, p. 996.

[29] See also the chapter by Bersin, "The Meerwein-Ponndorf Reduction and the Oppenauer Oxidation," p. 125.

[30] Bernhauer, *Gärungschemisches Praktikum*, 2nd ed., Springer, Berlin, 1939, pp. 214 ff.; and Bernhauer, *Ergeb. Enzymforsch.*, **7**, 246 (1938).

[31] Neuberg and Nord, *Biochem. Z.*, **96**, 158 (1919).

[32] Haworth, Heilbron, Jones, Morrison, and Polya, *J. Chem. Soc.*, **1939**, 128.



$$\begin{array}{c} H_2C{-}OH \\ | \\ HC{-}OH \\ | \\ HC{-}OH \\ | \\ R \end{array} \xrightarrow{-2[H]} \begin{array}{c} H_2COH \\ | \\ C{=}O \\ | \\ HCOH \\ | \\ R \end{array}$$

In general, the essential requirements for carrying out these bacterial dehydrogenations are sufficient aeration of the reaction mixture and the use of young active bacteria grown on neutral nutrient media. The duration of oxidation may be considerably shortened by rapid agitation of the fermenting material.

In considering the feasibility of fermentation processes[43] for production on a commercial or semicommercial scale, the environment of the active organism must be taken into account. Most bacteria and yeasts develop submerged in the fermentation medium, while the majority of molds and certain aerobic bacteria, particularly the genus *Acetobacter*, develop in a zoogleal mat or mycelial felt on the surface. Economically these latter organisms are much less efficient; the duration of fermentation must be longer in the absence of agitation of the reaction mixture and large areas must be devoted to surface cultures which produce comparatively small quantities of material.

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[33] Hermann and Neuschul, *Biochem. Z.*, **233**, 129 (1931).

[34] Whistler and Underkofler, *J. Am. Chem. Soc.*, **60**, 2507 (1938).

[35] Reichstein, *Helv. Chim. Acta*, **17**, 996 (1934).

[36] Böeseken and Leefers, *Rec. trav. chim.*, **54**, 861 (1935). Fulmer, Dunning, Guymon, and Underkofler, *J. Am. Chem. Soc.*, **58**, 1012 (1936). See also Bernhauer, *Gärungschemisches Praktikum*, 2nd ed., Springer, Berlin, 1939, p. 227.

[37] Fulmer, Dunning, and Underkofler, *Iowa State Coll. J. Sci.*, **13**, 279 (1939).

[38] Dunning, *Iowa State Coll. J. Sci.*, **14**, 24 (1939). Dunning, Fulmer, and Underkofler, *ibid.*, **15**, 39 (1940).

[39] Tilden, *J. Bact.*, **37**, 629 (1939).

[40] Maclay, Hann, and Hudson, *J. Am. Chem. Soc.*, **64**, 1606 (1942).

[41] Fulmer, Underkofler, and Bantz, *J. Am. Chem. Soc.*, **65**, 1425 (1943).

[42] Bernhauer and Görlich, *Biochem. Z.*, **280**, 367 (1935).

[43] Wells and Ward, *Ind. Eng. Chem.*, **31**, 172 (1939).

After investigating the possibility of adapting these aerobic processes to economical large scale production, May, Herrick, Moyer, and Wells[44] reported that submerged mold fermentations could be carried out successfully with modifications in the apparatus. The fermentation medium was contained in gas-washing bottles with sintered glass false bottoms. The bottles were placed in an autoclave at the desired temperature and at an increased air pressure, and the fine stream of bubbles passing up through the false bottoms aerated and gently agitated the reaction mixture. These experiments indicated that the increased pressure at which the apparatus could be employed materially increased the yield of fermentation products.

Herrick, Hellbach, and May[45] extended these investigations, and developed special equipment for adapting some of these aerobic processes for industrial use. This device has proved highly satisfactory for the production of *d*-lactic acid from glucose, 5-ketogluconic acid from gluconic acid, dihydroxyacetone from glycerol, and so on.[43] "The apparatus consists of a horizontally mounted rotary drum, which is constructed of very pure aluminum. To the inside of the shell are attached buckets which lift and drop the medium in thin layers as the drum revolves; the liquor and the organism are agitated thoroughly and exposed to the gaseous atmosphere prevailing within the fermenter. Provision is made for the controlled entrance and exit of sterile air, and the equipment may be operated at any desired pressure from atmospheric to as high as 3 or 4 atmospheres." Results have indicated that the use of increased pressure is very advantageous in certain fermentations. Reactions which require 10 to 20 days in surface cultures may be carried out in better yields in most cases in 18 to 35 hours in this fermentation apparatus.

OXIDATION OF SORBITOL TO SORBOSE I.[46] Technical grade of sorbitol syrup containing 75.7% sorbitol, 2.3% glucose, 0.6% sodium sulfate, and 21.4% water is diluted to a sorbitol concentration of 10% with distilled water. The rotary drum fermenter is charged with 3.2 liters of the medium to which 5 g. of Difco yeast extract per liter of solution and 200 ml. of a suspension of *Acetobacter suboxydans* have been added. (Wells *et al.*[46] give details for the preparation of a highly active inoculum.) Sterile air is passed through the apparatus which is maintained at 30°C. and is vigorously agitated for the 16 to 30 hours of fermentation. In order to follow the course of reaction, the sorbose content of samples removed at intervals during the fermentation is determined by copper reduction values with the method of Shaffer and Hartman.[47] When oxidation is complete, the liquor is clarified and concentrated *in vacuo* at 40° to 45°C. Almost pure sorbose crystallizes from the concentrate in over 80% yield.

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[44] May, Herrick, Moyer, and Wells, *Ind. Eng. Chem.*, **26**, 575 (1934).
[45] Herrick, Hellbach, and May, *Ind. Eng. Chem.*, **27**, 681 (1935).
[46] Wells, Stubbs, Lockwood, and Roe, *Ind. Eng. Chem.*, **29**, 1385 (1937).
[47] Shaffer and Hartman, *J. Biol. Chem.*, **45**, 365 (1921).

Other experiments[48] indicated that a sorbitol concentration of 20% is most satisfactory for large scale runs, with yields in excess of 90%. In some cases the conversion is almost quantitative in as short a fermentation time as 16 hours if a very high degree of aeration and great agitation are maintained during the fermentation.

In an investigation of the laboratory scale preparation of sorbose, Fulmer *et al.*[49] concluded, as had earlier workers, that although various species of the genus *Acetobacter*, such as *A. aceti*, *A. suboxydans*, *A. gluconicum*, *A. xylinum*, and others, are capable of effecting the oxidation, *A. suboxydans* is the most satisfactory. The rate of fermentation and the final yield are greater with this organism than with *A. xylinum* and some of the other bacteria which have greater oxidizing power, and consequently carry the oxidation beyond the desired stage.[50] In contrast to earlier research in which the concentration of sorbitol was 3 to 6% these workers found that the final, 80% yield was independent of the concentration of the starting material up to a concentration of 35% even though the rate of attaining this final yield decreased with increasing concentration. However, the activity of the organism is negligible at concentrations of sorbitol of 40% or over. After 7 to 12 days of fermentation a yield of 28 g. of sorbose of 95% purity is obtained from one hundred milliliters of a 35% solution of sorbitol.

OXIDATION OF SORBITOL TO SORBOSE II.[49] The medium (100 ml.) containing 15.4 g. of sorbitol and 0.5 g. of yeast extract in a 300 ml. Erlenmeyer flask is fermented by *A. suboxydans* at 25° to 30°C. without any agitation, since disturbing the mixture appears to lower the yield. After 7 to 12 days the medium is filtered, and the filtrate evaporated *in vacuo* to a small volume and allowed to crystallize. The first fraction is 95% pure and may be recrystallized from the minimum quantity of water.[51]

The use of *A. xylinum* for the conversion of glycerol to dihydroxy acetone was first reported by Bertrand,[52] and was further investigated by Fischer and Mildbrand[53] and Bernhauer and Schoen.[54] In addition to this bacterium, *A. dioxyacetonicum*[55] and *A. suboxydans*[56-58] have been employed for carrying out the same transformation. The optimum conditions for the preparation and isolation of dihydroxyacetone produced by the action of *A. suboxydans* on glycerol have been worked out by Underkofler and Fulmer.[59]

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[48] Wells, Lockwood, Stubbs, Roe, Porges, and Gastrock, *Ind. Eng. Chem.*, **31**, 1518 (1939).

[49] Fulmer, Dunning, Guymon, and Underkofler, *J. Am. Chem. Soc.*, **58**, 1012 (1936).

[50] Kluyver and de Leeuw, *Tijdschr. vergelijk. Geneeskunde*, **10**, 170 (1924); *Chem. Abstracts*, **18**, 3202 (1924).

[51] This same oxidation with a 3% sorbitol solution and *Acetobacter suboxydans* was carried out on a laboratory scale in special apparatus by Böeseken and Leefers, *Rec. trav. chim.*, **54**, 861 (1935).

[52] Bertrand, *Compt. rend.*, **122**, 900 (1896); **126**, 984 (1898); *Ann. chim. phys.*, **8**, 3 (1904); *Bull. soc. chim.*, **15**, 627 (1896); **19**, 502 (1898).

[53] Fischer and Mildbrand, *Ber.*, **57**, 707 (1924).

[54] Bernhauer and Schoen, *Z. physiol. Chem.*, **177**, 107 (1928).

OXIDATION OF GLYCEROL TO DIHYDROXYACETONE.[59] 100 ml. of the medium, which for optimum results must have a pH range of 5.5 to 7.0 and contain 0.5% of yeast extract (Difco powdered product), 6% of glycerol, and 0.10 to 0.30% of potassium dihydrogen phosphate, are placed in a 300 ml. Erlenmeyer flask and inoculated with 3 ml. of an active (24 to 72 hour) culture of *A. suboxydans*. The fermentation is best carried out at 28° to 30°C. for a maximum of 7 days.

The best yields of crystalline dihydroxyacetone are obtained by the following procedure. To 1 liter of the fermented medium (the combined liquors from ten runs) are added 10 g. each of animal charcoal, calcium carbonate, and kieselguhr. The medium is shaken, filtered, evaporated *in vacuo* to one-seventh of the volume, 3 to 4 volumes of absolute alcohol are added with stirring, and the mixture is filtered. The solution is evaporated *in vacuo* and the remaining syrup poured with vigorous stirring into 10 volumes of acetone. After standing overnight, Norite is added, the solution is filtered, and the clear filtrate is evaporated *in vacuo* as far as possible. Although crystallization may be accelerated by seeding, the thick syrup will crystallize spontaneously after removal of the residual solvent in a vacuum desiccator. The crystal mass is triturated with cold absolute alcohol, and filtered and washed with cold absolute alcohol until pure white crystals are obtained. After a similar treatment of the mother liquor, the yield of dihydroxyacetone is 80% of the quantity determined according to the reducing power (about 75% of the theoretical). A further purification can be achieved through crystallization from acetone.[60]

IV. OXIDATION OF ALDEHYDES TO ACIDS

Since oxidation of aldehydes to acids occurs during the digestion of food, the process has been observed in numerous organisms and has been carried out with many aldehydes. Various enzyme preparations obtained from bacteria, fungi, higher plants, or animal organs which are involved in the catalysis of this oxidation have been studied. For example, there have been numerous investigations of the aldehyde-oxidizing Schardinger enzyme from fresh milk. Without treating the enzymic chemical problem in more detail, it may be mentioned that the prosthetic group is known for some of these dehydrogenases. The dehydrogenase from yeast and from animal tissue which changes triose phosphate into phosphoglyceric acid is known to act with codehydrogenase I; the glucose dehydrogenase from liver can use codehydrogenase I as well as codehydrogenase II; the hexose monophosphate dehydrogenase from yeast or red blood cells contains codehydrogenase II as the dissociating group.[61]

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[55] Virtanen and Bärlund, *Biochem. Z.*, 169, 169 (1936).

[56] visser't Hooft, *Biochemische onderzoekingen over het Geslacht Acetobacter*, Thesis, Delft, 1925.

[57] Virtanen and Nordlund, *Biochem. J.*, 27, 442 (1933).

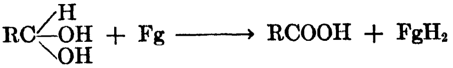
[58] Neuberg and Hoffman, *Biochem. Z.*, 279, 318 (1935).

[59] Underkofler and Fulmer, *J. Am. Chem. Soc.*, 59, 301 (1937).

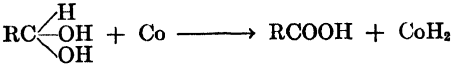
[60] See also Bernhauer, *Gärungschemisches Praktikum*, 2nd ed., Springer, Berlin, 1939, p. 228.

It has been shown recently that two of these aldehyde dehydrogenases are flavin enzymes; that is, enzymes which contain riboflavin as the prosthetic group, and which do not require an easily dissociating codehydrogenase. Pure preparations of the glucose dehydrogenase from the molds *Aspergillus niger* and *Penicillium glaucum* contain a flavin group. The higher the concentration of this group, the more active are the preparations.[62] Separation and further purification of this flavin group have not yet been described. Furthermore, the aldehyde dehydrogenase from liver has been characterized as a flavoprotein with the dinucleotide from riboflavinphosphoric acid and adenylic acid as the prosthetic group.[63]

According to these observations the aldehyde dehydrogenase may either catalyze the oxidation-reduction between aldehydes (formulated as hydrates) and the flavin group (Fg) without assistance of an easily dissociated codehydrogenase (Equation 7), or the hydrogen may be carried by the codehydrogenase (Equation 8), and from it to the flavin group of the flavoprotein (Equation 9). When carrying out the reaction for preparative purposes acetic acid-forming bacteria are used.[64]



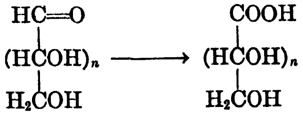
$$\mathrm{RC}\begin{matrix}\diagup \mathrm{H}\\ -\mathrm{OH}\\ \diagdown \mathrm{OH}\end{matrix} + \mathrm{Fg} \longrightarrow \mathrm{RCOOH} + \mathrm{FgH_2} \tag{7}$$



$$\mathrm{RC}\begin{matrix}\diagup \mathrm{H}\\ -\mathrm{OH}\\ \diagdown \mathrm{OH}\end{matrix} + \mathrm{Co} \longrightarrow \mathrm{RCOOH} + \mathrm{CoH_2} \tag{8}$$

$$\mathrm{CoH_2} + \mathrm{Fg} \longrightarrow \mathrm{Co} + \mathrm{FgH_2} \tag{9}$$

Exhaustive investigations have been made on the conversion of aldoses to aldonic acids. Glucose is transformed into gluconic acid in 70 to



$$\begin{array}{c}\mathrm{HC{=}O}\\ |\\ \mathrm{(HCOH)_n}\\ |\\ \mathrm{H_2COH}\end{array} \longrightarrow \begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{(HCOH)_n}\\ |\\ \mathrm{H_2COH}\end{array}$$

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[61] Fischer, *Ergeb. Enzymforsch.*, **8**, 185 (1939).

[62] Franke and Deffner, *Ann.*, **541**, 117 (1939).

[63] Subrahmanyan, Green, and Gordon, *Nature*, **144**, 1016 (1939).

[64] Bernhauer, *Ergeb. Enzymforsch.*, **7**, 257 (1938). Bernhauer, *Gärungschemisches Praktikum*, 2nd ed., Springer, Berlin, 1939, pp. 230 ff.

80% yield with *Acetobacter suboxydans* or *A. xylinum*.[65] Galactose and mannose are converted to *d*-galactonic acid and *d*-mannonic acid, respectively, with substrate-trained *A. gluconicum*. The pentoses *l*-arabinose and *l*-xylose are oxidized satisfactorily by bacteria to *l*-arabinonic acid and *l*-xylonic acid.

However, for the formation of gluconic acid from glucose, *Acetobacter* is less effective than mold. Most of the acid-forming aspergilli and other mycelium molds oxidize glucose in this way. Many bring about the conversion in good yield only in buffered media (the acid resulting from the reaction is fixed with calcium carbonate), while others act best in acid solutions.

The most effective technical process involves the use of submerged mycelium mold as the fermenting agent, with extensive aeration and stirring in a rotating ferment drum in the same way as described for the preparation of sorbose. By the use of *Asperillus niger* cultures, which have been agitated in a particular fashion until germination of the spores, 91 kg. of glucose in 530 liters of medium may be oxidized to gluconic acid in less than 24 hours. The yield amounts to 95% on the basis of the sugar used as starting material and 97% of that fermented.[66] Mannose and galactose have also been oxidized by molds.[67]

V. HYDROGENATION OF ETHYLENIC COMPOUNDS

1. General Considerations

The enzymic hydrogenation of ethylenic compounds as a general reaction was discovered in studying the action of fermenting yeasts on unsaturated α-keto acids. Besides the expected decarboxylation and reduction of the resulting aldehyde to the olefinic alcohol, the formation of the corresponding saturated alcohol also occurred.[68] Investigations of biochemical hydrogenation of the C—C double bond were then extended to unsaturated aldehydes, ketones, and primary alcohols, and the reduction was carried out with ferment solutions. Furthermore it can be shown that bacteria are also capable of this type of hydrogenation and that the saturation of certain ethylenic compounds occurs in the animal organism.

It is postulated from the evidence of the majority of cases investigated that the biological hydrogenation of an ethylenic compound will occur in a position α,β to a carbonyl or primary hydroxyl group. Neither olefinic alcohols and ketones, whose ethylenic linkage is isolated from the functional group, nor olefinic acids and secondary alcohols, even when unsaturated in the α,β position, are attacked by fermenting yeast. The conditions for hydrogenation in the animal organism and by bacteria have not been investigated sufficiently to allow generalizations. Individual examples are mentioned in the following sections.

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[65] See for example: Porges, Clarke, and Gastrock, *Iowa State Coll. J. Sci.*, **16**, 451 (1942); *Ind. Eng. Chem.*, **32**, 107 (1940); Stubbs, Lockwood, Roe, Tabenkin, and Ward, *ibid.*, **32**, 1626 (1940).

[66] Gastrock, Porges, Wells, and Moyer, *Ind. Eng. Chem.*, **30**, 782 (1938).

[67] Reports on the preparation and use of glucose oxidase preparations are found in Müller, *Ergeb. Enzymforsch.*, **5**, 270 (1936), and Franke and Deffner, *Ann.*, **541**, 117 (1939); data for carrying out experiments with *Acetobacter* and mold for the preparation of gluconic acid are found in Bernhauer, *Gärungschemisches Praktikum*, 2nd ed., Springer, Berlin, 1939, pp. 230 ff. and 237 ff.

[68] Fischer and Wiedemann, *Ann.*, **513**, 260 (1934).

The enzymic processes which take place in an ethylenic hydrogenation have been clarified only in the case of yeast enzymes.[69] The observation that the reduction of an olefinic alcohol in sugar-free yeast suspension occurs only very slowly, and fails to take place almost entirely if the yeast has been deprived of carbohydrate reserve by longer aeration leads to the conclusion that the process is closely linked to the oxidation-reduction in carbohydrate breakdown. The dependence of the hydrogenation on the acidity of the ferment solution is again related to the carbohydrate metabolism. For example, with fresh brewers' yeast the velocity of the hydrogenation of cinnamyl alcohol in a fermenting solution buffered to pH 4.5 to 8.5 increases continuously with increasing alkalinity. As is known, disproportionation in carbohydrate decomposition is also more pronounced with an increase in pH. Consequently in a solution of pH 8.5 the normal formation of ethyl alcohol is suppressed and glycerol results principally from the triose, and acetic acid together with alcohol, from acetaldehyde. In alkaline medium, the equilibrium in the oxidation-reduction reaction between triose or alcohol on the one hand and codehydrogenase on the other is displaced strongly in favor of the codehydrogenase[70] so that to a certain extent more "fermentation hydrogen" is at the disposal of the dihydrocodehydrogenase for other reactions.

From experiments with purified enzyme preparations from yeast[71] it appears that in addition to a codehydrogenase-reducing system (Eq. 10) the presence of a flavin enzyme is also necessary (Eq. 11) for saturating the olefin (Eq. 12). Accordingly, the dihydrocoenzyme must next undergo an

$$\mathrm{AH_2} + \mathrm{Co} \xrightleftharpoons{\text{Protein A}} \mathrm{A} + \mathrm{CoH_2} \tag{10}$$

$$\mathrm{CoH_2} + \mathrm{Fg} \xrightleftharpoons[\text{flavin enzyme}]{\text{Protein of}} \mathrm{Co} + \mathrm{FgH_2} \tag{11}$$

$$\mathrm{FgH_2} + \mathrm{{>}C{=}C{<}} \xrightarrow[\text{dehydrogenase}]{\text{Ethylene}} \mathrm{Fg} + \mathrm{{>}CHCH{<}} \tag{12}$$

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[69] Fischer and Eysenbach, *Ann.*, **529,** 87 (1937). Fischer and Eysenbach, unpublished work. See Eysenbach, *Enzymatische Hydrierungen ungesättigter Verbindungen,* Dissertation, Freiburg, 1937.

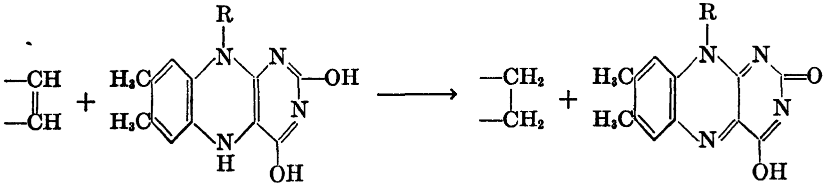
[70] Euler, Adler, and Hellström, *Z. physiol. Chem.*, **241,** 239 (1936).

[71] Fischer and Eysenbach, *Ann.*, **529,** 87 (1937).

oxidation-reduction with a flavin group before the hydrogen adds to the ethylene bond. The great instability of the ethylene dehydrogenase has hindered its purification. The decomposition of the protein component and more accurate characterization of the flavin prosthetic group have not been successful. Therefore, it is still undetermined whether the reaction of Equation 11 is catalyzed by the same protein as that required for Equation 12 or whether the oxidation-reduction between codehydrogenase and the alloxazine derivative of another protein component is as effective as that between alloxazine and the ethylenic compound.

As a result, questions concerning the specific role of the ethylenic dehydrogenase are unanswered. The separation and further purification of the flavin group from the active protein and its characterization as an alloxazine adenine dinucleotide[72] have been successful only in the case of a special ethylenic hydrogenase, fumaric hydrogenase,[73] which is capable of irreversibly hydrogenating fumaric acid.

The ethylenic double bond is reduced by hydrogen from the isoalloxazine nucleus of leucoflavoprotein.



The method of carrying out zymochemical hydrogenation of ethylenic bonds is fundamentally the same as that for the reduction of the carbonyl group: the unsaturated substance, in solution or finely dispersed, is stirred with a suspension of the fermenting microorganisms in a sugar solution. Intensive agitation of the fermentation system considerably shortens the reaction time.

2. Hydrogenations with Yeast

A. Primary Alcohols

The hydrogenation of α,β-unsaturated primary alcohols[68] proceeds most rapidly with compounds which are slightly or only moderately water-soluble. 50% of the crotyl alcohol (Ia) as a 1% solution of the alcohol in an active fermentation sediment (with about 3% dry weight of brewers' yeast) is reduced to butyl alcohol (Ib) in the course of a day.

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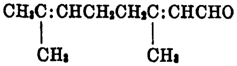
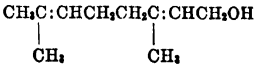
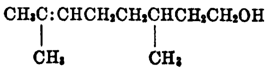
[72] Fischer, Roedig, and Rauch, *Naturwissenschaften*, **27**, 197 (1939); *Ann.*, **552**, 203 (1942).

[73] Fischer and Eysenbach, *Ann.*, **530**, 99 (1937).

$$RCH{=}CHCH_2OH \xrightarrow{+2H^+\ (+2e)} RCH_2CH_2CH_2OH$$

With a fermentation period of 2 to 3 days, the hydrogenation is more complete, but the yield of saturated alcohol is smaller, probably because of assimilation by the yeast. Cinnamyl alcohol (IIa) is converted to hydrocinnamyl alcohol (IIb) almost as quickly, while the hydrogenation of 2-methyl-2-buten-1-ol (IIIa) to *l*-2-methylbutan-1-ol requires twice as long. Apparently a substituent on the ethylenic group retards its saturation. Since an ethylenic bond, unless it is conjugated with a hydroxyl group, is not hydrogenated by yeast, there is the possibility of saturating a double bond adjacent to an alcohol group with fermenting yeast and leaving an isolated double bond intact. An example of such a reaction is the reduction of geraniol (IVa) to *d*-citronellol (IVb); this hydrogenation goes no further even with greatly increased fermentation time. As would be expected, yeast affects neither citronellol (IVb) nor the easily water-soluble, unsubstituted 3-buten-1-ol (VII).

In unsaturated alcohols containing two or three conjugated double bonds, such as sorbyl alcohol (Va) and the octatrienol (VIa), the zymochemical hydrogenation also stops after saturating only the double bond adjacent to the hydroxyl group. The hydrogenated compounds resulting in 50 to 70% yield were shown, by oxidative decomposition, to be exclusively 4-hexen-1-ol (Vb) and 4,6-octadien-1-ol (VIb).[74]

$CH_3CH{:}CHCHO$ (I) Crotonaldehyde	$CH_3CH{:}CHCH_2OH$ (Ia) Crotyl alcohol	$CH_3CH_2CH_2CH_2OH$ (Ib) Butyl alcohol
$C_6H_5CH{:}CHCHO$ (II) Cinnamaldehyde	$C_6H_5CH{:}CHCH_2OH$ (IIa) Cinnamyl alcohol	$C_6H_5CH_2CH_2CH_2OH$ (IIb) Hydrocinnamyl alcohol
$CH_3CH{:}C(CH_3)CHO$ (III) Tiglaldehyde	$CH_3CH{:}C(CH_3)CH_2OH$ (IIIa) 2-Methyl-2-buten-1-ol	$CH_3CH_2CH(CH_3)CH_2OH$ (IIIb) 2-Methyl-1-butanol
 $CH_3\underset{\displaystyle CH_3}{C}{:}CHCH_2CH_2\underset{\displaystyle CH_3}{C}{:}CHCHO$ (IV) Citral	 $CH_3\underset{\displaystyle CH_3}{C}{:}CHCH_2CH_2\underset{\displaystyle CH_3}{C}{:}CHCH_2OH$ (IVa) Geraniol	 $CH_3\underset{\displaystyle CH_3}{C}{:}CHCH_2CH_2\underset{\displaystyle CH_3}{CH}CH_2CH_2OH$ (IVb) Citronellol
$CH_3CH{:}CHCH{:}CHCHO$ (V) Sorbaldehyde	$CH_3CH{:}CHCH{:}CHCH_2OH$ (Va) Sorbyl alcohol	$CH_3CH{:}CHCH_2CH_2CH_2OH$ (Vb) 4-Hexen-1-ol
$CH_3CH{:}CHCH{:}CHCH{:}CHCHO$ (VI) 2,4,6-Octatrienal	$CH_3CH{:}CHCH{:}CHCH{:}CHCH_2OH$ (VIa) 2,4,6-Octatrien-1-ol	$CH_3CH{:}CHCH{:}CHCH_2CH_2CH_2OH$ (VIb) 4,6-Octadien-1-ol
$CH_2{:}CHCH_2CH_2OH$ (VII) 3-Buten-1-ol		

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[74] Fischer and Wiedemann, *Ann.*, **522**, 1 (1936).

Conjugated systems are hydrogenated only in the α,β position without the possibility of a terminal reduction. This specificity of zymochemical hydrogenation is not achieved by other methods.

B. Aldehydes[68]

The addition of hydrogen to the carbonyl group of α,β-unsaturated aldehydes takes place independently of reduction at the ethylenic linkage. But since carbonyl reduction proceeds more rapidly, at least with the use of live fermenting yeast, it is assumed that the olefinic aldehydes after first being transformed into the alcohols undergo a hydrogenation of the ethylenic linkage (Eq. 13). The final products of yeast action are in any case the

$$RCH{=}CHCHO \xrightarrow{+2H^+ (+2e)} RCH{=}CHCH_2OH \xrightarrow{+2H^+ (+2e)} RCH_2CH_2CH_2OH \quad (13)$$

same as from the corresponding unsaturated alcohols. Crotonaldehyde (I), tiglaldehyde (III), citral (IV), cinnamaldehyde (II), sorbaldehyde (V), and 2,4,6-octatrienal (VI) give the corresponding saturated alcohols (Ib) to (VIb). With the polyene aldehydes, as with the polyene alcohols, α,β hydrogenation results exclusively.[74]

Side reactions occur to a greater degree with the lower aliphatic aldehydes than with the alcohols. These reactions are probably due to assimilation of the reaction components by the yeast cells. In any case, the yield of saturated alcohol is inferior (20 to 60%) to that obtained from the olefinic alcohol. A Cannizzaro disproportionation is not observed to any great extent.

HYDROGENATION OF SORBALDEHYDE TO 4-HEXEN-1-OL.[68] A solution of 25 g. of sorbaldehyde and 70 g. of sugar in 2.5 liters of water is added dropwise over a period of 3 hours to the fermentation sediment from 1.5 liters of yeast mash. After 20 hours a further 0.5 liter of yeast is introduced, and 300 g. more of sugar is added during the course of the reaction (4 days). After steam-distilling, 12 g. of crude product, consisting essentially of 4-hexen-1-ol, b.p. 156° to 158°C., results.

In other experiments, carried out for a shorter time, 10 to 20% of sorbyl alcohol, b.p. 160° to 163°C., was obtained. The alcohol can be separated from the aldehyde by careful fractionation through a Widmer column.

C. Ketones[75]

In α,β-unsaturated ketones, the hydrogenations of both the carbonyl group and the ethylenic bond proceed simultaneously as independent reactions. The velocities of the reductions are much smaller throughout than with olefinic aldehydes, and the equilibria are displaced very unfavorably toward the carbonyl reduction (Eq. 14). Consequently the corresponding saturated ketone (*a*) is formed in the largest quantity; the reduction of the carbonyl group then proceeds as a second reaction which yields a greater proportion of the saturated alcohol (*b*) if the experiments are carried out for a longer time.

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[75] Fischer and Wiedemann, *Ann.*, **520**, 52 (1935).

$$\mathrm{RCH{=}CHCOR} - \begin{cases} \longrightarrow \underset{(a)}{\mathrm{RCH_2CH_2COR}} \longrightarrow \underset{(b)}{\mathrm{RCH_2CH_2CHOHR}} \\ \longrightarrow \underset{(c)}{\mathrm{RCH{=}CHCHOHR}} \end{cases} \qquad (14)$$

Saturation of the ethylenic bond takes place most rapidly, however, in a ketone whose double bond, conjugated with the carbonyl group, lies between secondary carbon atoms. Benzylideneacetone (VIII) can be hydrogenated almost completely in a 5 to 10 day fermentation experiment, while the more water-soluble furfurylideneacetone (IX) and more highly unsaturated furan derivatives such as furfurylidenecrotylideneacetone can be hydrogenated even more rapidly. The doubly unsaturated crotylideneacetone (X) adds 2 hydrogen atoms in the α,β position in 4 to 6 days of fermentation. Although cinnamylideneacetone (XI) is also reduced, the reaction is less complete because of the insolubility of the ketone in water. Ketones in which the ethylenic bond is attached to a tertiary carbon atom are reduced considerably more slowly and as a result have reacted only very slightly in the usual fermentation time of one week. It appears to be immaterial whether the ethylenic bond is in the aliphatic chain or in a hydroaromatic ring. Mesityl oxide (XII), 3-methyl-2-cyclohexenone (XIII), pulegone (XIV), and carvone (XV) are hydrogenated only to a

$\mathrm{C_6H_5CH{=}CHCOCH_3}$
(VIII) Benzylideneacetone

$\mathrm{C_6H_5CH_2CH_2COCH_3}$
(VIIIa) Benzylacetone

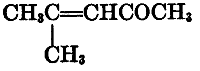
$\mathrm{C_6H_5CH_2CH_2CHOHCH_3}$
(VIIIb) 4-Phenyl-2-butano

$\mathrm{C_6H_5CH{=}CHCHOHCH_3}$
(VIIIc) 4-Phenyl-3-buten-2-ol

$\mathrm{CH_3CH{=}CHCH{=}CHCOCH_3}$
(X) Crotylideneacetone

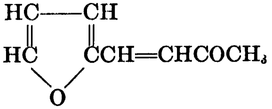
$\mathrm{CH_3CH{=}CHCH_2CH_2COCH_3}$
(Xa) 5-Hepten-2-one

$\mathrm{CH_3CH{=}CHCH_2CH_2CHOHCH_3}$
(Xb) 5-Hepten-2-ol



$\mathrm{CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CHCOCH_3}$

(XII) Mesityl oxide



(IX) Furfurylideneacetone

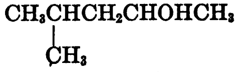
$\mathrm{C_4H_3OCH_2CH_2COCH_3}$
(IXa) Furfurylacetone

$\mathrm{C_4H_3OCH_2CH_2CHOHCH_3}$
(IXb) 1-Furfuryl-2-propanol

$\mathrm{C_6H_5CH{=}CHCH{=}CHCOCH_3}$
(XI) Cinnamylideneacetone

$\mathrm{C_6H_5CH{=}CHCH_2CH_2COCH_3}$
(XIa) Cinnamylacetone

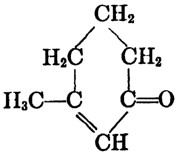
$\mathrm{C_6H_5CH{=}CHCH_2CH_2CHOHCH_3}$
(XIb) 1-Cinnamyl-2-propanol



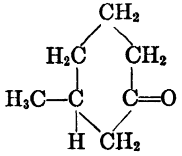
$\mathrm{CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CHOHCH_3}$

(XIIb) 4-Methyl-2-pentanol

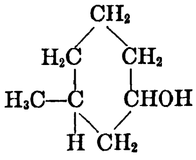
small extent after 7 days fermentation. The inhibiting action of branched chains is also observed with olefinic aldehydes although it is not so marked.



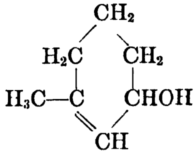
(XIII) 3-Methyl-2-cyclohexenone



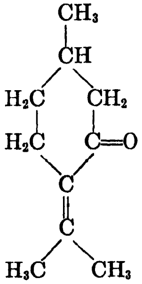
(XIIIa) 3-Methylcyclohexanone



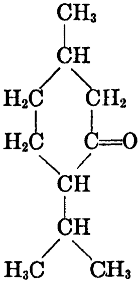
(XIIIb) 3-Methylcyclohexanol



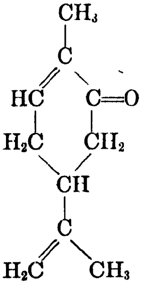
(XIIIc) 3-Methyl-2-cyclohexenol



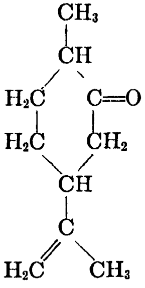
(XIV) Pulegone



(XIVa) Menthone



(XV) Carvone



(XVa) Dihydrocarvone

$CH_2{=}CHCH_2CH_2COCH_3$

(XVI) Allylacetone

If the ethylenic linkages of ketones are in isolated positions, they remain completely unreduced. Allylacetone (XVI) is hydrogenated only at the carbonyl group even after long fermentation; with crotylideneacetone (X) and cinnamylideneacetone (XI) the addition of hydrogen stops after saturating the α,β bond.[74]

In olefinic ketones the ratio of the velocities of carbonyl and C—C double bond hydrogenation is quite different from that in olefinic aldehydes. After a week of fermentation the reaction products from the ketones VIII through XV consisted of 80 to 95% of the corresponding hydrogenated ketones VIIIa through XVa, and only 20 to 5% of the hydrogenated alcohols VIIIb through XVb.

Secondary olefinic alcohols (Eq. 14c, p. 177) evidently are not formed from most α,β-unsaturated ketones. The exclusive addition to the carbonyl group occurs only in exceptional cases and to a limited extent in comparison with the preponderant addition to the C—C double bond. With benzylideneacetone (VIII) uniquely, the alcohol fraction, which is only about 5% of the total reaction product from the reduction of VIII, contains one-third olefinic alcohol VIIIc and two-thirds saturated alcohol VIIIb.

This carbonyl reduction in α,β-unsaturated ketones proceeds with more difficulty than the carbonyl reduction in the corresponding saturated ketones. Conjugation with an ethylenic bond therefore greatly reduces the velocity of the yeast reduction of a carbonyl group. If the ethylenic bonds of α,β-unsaturated ketones such as pulegone (XIV) and carvone (XV) are difficultly hydrogenated by enzymic action, reduction does not occur at the carbonyl group. Further examples are found in certain of the steroid hormones (see p. 187). An isolated double bond, on the contrary, does not hinder carbonyl reduction.

As formulated on page 177, the saturated secondary alcohol (Eq. 14*b*) results only from the hydrogenated ketone (*a*). Apparently the theoretically possible formation from the secondary olefinic alcohol (*c*) does not take place, since the hydrogenation of such compounds as (*c*) with fermenting yeast has not yet been successful.

D. Keto Acids

In general, α,β-unsaturated keto acids decompose under the action of fermenting yeast in the following way[68]:

$$\mathrm{RCH{=}CHCOCOOH} \longrightarrow \mathrm{RCH{=}CHCHO} + \mathrm{CO_2}$$

$$\mathrm{RCH{=}CHCHO} \xrightarrow{+2\mathrm{H}^+\,(+2e)} \mathrm{RCH{=}CHCH_2OH} \xrightarrow{+2\mathrm{H}^+\,(+2e)} \mathrm{RCH_2CH_2CH_2OH}$$

First, the fermentative decarboxylation of the substituted pyruvic acid takes place (as in saturated α-keto acids); the resulting unsaturated aldehydes are transformed into olefinic alcohols and finally into saturated alcohols (as previously described in the section on aldehydes). The formation of olefinic aldehydes is not carried out directly, since dry yeast does not induce decarboxylation of the unsaturated keto acids and living yeast reduces directly to the olefinic alcohol. With the use of fresh yeast which has been reduced in strength, a disproportionation occurs, resulting in the production of equimolecular quantities of olefinic alcohol and olefinic acid in addition to carbon dioxide.

$$\mathrm{2RCH{=}CHCOCOOH} + \mathrm{H_2O} \longrightarrow \mathrm{RCH{=}CHCH_2OH} + \mathrm{RCH{=}CHCOOH} + \mathrm{2CO_2}$$

For example, through the action of strongly fermenting yeast, pure hydrocinnamyl alcohol is formed in 75% yield from benzylidenepyruvic acid (XVII) and 4,6-octadien-1-ol (identical with that from 2,4,6-octatrienal and 2,4,6-octatrien-1-ol[74]) in 60% yield from sorbylidenepyruvic acid (XVIII).

$$C_6H_5CH{=}CHCOCOOH \longrightarrow C_6H_5CH_2CH_2CH_2OH$$

(XVII) Benzylidenepyruvic acid — Hydrocinnamyl alcohol

$$CH_3CH{=}CHCH{=}CHCH{=}CHCOCOOH \longrightarrow$$

(XVIII) Sorbylidenepyruvic acid

$$CH_3CH{=}CHCH{=}CHCH_2CH_2CH_2OH$$

4,6-Octadien-1-ol

The preparative possibilities of ethylenic hydrogenation by fermenting yeast have already been demonstrated. In individual cases the zymochemical hydrogenation of an olefinic alcohol or olefinic ketone may be desirable to avoid attacking other sensitive places in the molecule. For example, furfurylideneacetone (IX), which adds hydrogen only to the side-chain ethylenic bond and then to the carbonyl group through the action of yeast, undergoes cleavage of the furan ring with catalytic hydrogenation.

Fermentative hydrogenation is most valuable, however, for the formation of an optically active hydrogenated product or for the partial reduction of a polyethylenic alcohol or ketone. Optically active compounds result from the saturation of an ethylenic bond attached to secondary carbon atoms with different substituents; for example, geraniol yields (+)-citronellol. Since hydrogenation of poly-unsaturated alcohols and ketones occurs exclusively in the α,β position, 2,4,6-octatrien-1-ol yields 4,6-octadien-1-ol. In both these cases zymochemical hydrogenations are successful where non-enzymic methods fail.

HYDROGENATION OF SORBYLIDENEPYRUVIC ACID TO 4,6-OCTADIEN-1-OL.[68] A solution of sugar and the sodium salt from 8.5 g. of the keto acid in 1.3 liters of water is added slowly to 1.5 liters of fresh yeast. It is necessary to add yeast three times (about 1 liter) after 4, 22, and 30 hours and a total of 600 g. of sugar in order to maintain active fermentation for 46 hours. In this way 3.8 g. (60%) of pure 4,6-octadien-1-ol boiling at 101° to 102°C. at 14 mm. is obtained as an oily distillate.

3. Hydrogenations with Bacteria

The saturation of ethylenic compounds by bacterial fermentation has not yet undergone a systematic investigation, either with reference to its scope or to the most suitable variety of bacteria. But, from different examples, it appears that double bonds which are not accessible to hydrogenation by yeast are attacked by bacteria. The first observation that such a reaction might be a general one was made by Linneweh who transformed crotonobetaine (XIX) and also carnitine (XIXa) into γ-butyrobetaine (XIXb) with saprophytic microörganisms.[76]

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[76] Linneweh, *Z. physiol. Chem.*, **181,** 54 (1929).

$$(CH_3)_3\overset{+}{N}CH_2CH{=}CHCOO^-$$
(XIX)

$$(CH_3)_3\overset{+}{N}CH_2CHOHCH_2COO^-$$
(XIXa)

$$(CH_3)_3\overset{+}{N}CH_2CH_2CH_2COO^-$$
(XIXb)

Crotyl alcohol is hydrogenated to butyl alcohol by fermenting colon bacteria.[77] Since the reaction proceeds most rapidly at a pH of 7 to 8, it is necessary to buffer the acid resulting from the *Escherichia coli* fermentation.

Hydrogenation of olefinic acids, such as oleic and sorbic acids, by different bacteria (*E. coli, Bacillus subtilis, B. fluorescens,* etc.) has been observed but no characterization of the reaction products was made.[78] Several examples of the hydrogenation of unsaturated steroids by a bacillus of the *B. putrificus* type are mentioned on page 192.

The scope of bacterial metabolism appears to warrant further investigations of bacterial hydrogenation.

4. Hydrogenations in the Animal Organism

The hydrogenation of olefins in the course of animal metabolism has been directly demonstrated.[79] However, since oxidative decomposition predominates in most cases, these observations have not led to results of use in synthetic work. The urine of experimental animals has yielded relatively few substances produced by the reduction of ingested olefins, and these products were recovered in yields of not more than 10 to 30%.

The effect of animal metabolism on various unsaturated alcohols and ketones has also been investigated. The urine of rabbits fed geraniol (IVa) was found to contain the oxidation products citral (IV) and $HOOCC(CH_3){=}CHCH_2CH_2C(CH_3){=}CHCOOH$, as well as $HOOCC(CH_3){=}CHCH_2CH_2CH(CH_3)CH_2COOH$, produced by saturation of the double bond of geraniol followed by oxidation.[80] In another series of experiments, geraniol injected into rabbits gave the same two acids mentioned above in 16% yield and in a ratio of 2 parts of the diene acid to 1 part of the ethylenic acid. Upon oral administration the yield was higher (25 to 30%) and the ratio of the two products reversed.[81] When rabbits were fed various aromatic aliphatic ketones, the ketones which escaped complete oxidation were excreted chiefly as optically active carbinols in which one ethylenic bond was saturated. The alcohols were usually dextrorotatory, as are those produced by yeast action. In the hydrogenation of a conjugated system of double bonds, only the double bond α,β to a carbonyl group was reduced.[81]

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[77] Fischer and Robertson, *Ann.*, **529**, 84 (1937).

[78] Schönbrunner, *Biochem. Z.*, **304**, 26 (1940).

[79] For a bibliography, see Fischer, "Biochemische Hydrierungen," in *Fortschritte der Chemie organischer Naturstoffe*, Vienna, 1939, Vol. III, p. 45.

[80] Kuhn, F. Koehler, and L. Koehler, *Z. physiol. Chem.*, **242**, 171 (1936).

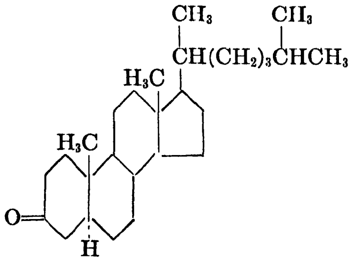
[81] Fischer and Bielig, *Z. physiol. Chem.*, **266**, 73 (1940).

VI. HYDROGENATIONS AND DEHYDROGENATIONS IN THE STEROID SERIES

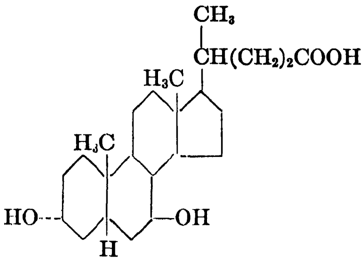
The different groups of naturally occurring steroids include many compounds which are interconvertible through simple oxidation and reduction of hydroxyl and carbonyl groups or by hydrogenation of the ethylenic bonds.

1. Sterols and Bile Acids

The dehydrogenation of the hydroxyl group in sterols by yeast and bacteria has not been successful in many cases. Recently, however, the oxidation of cholesterol (XXII) to Δ^4-cholestenone (XXIII) in 45% yield by *Proactinomyces erythropolis* has been reported.[82] The hydrogenation of the carbonyl group of cholestanone (XX) has not been achieved by yeast or bacteria.[83]



(XX) Cholestanone



(XXI) Cholic acid

The biological transformation of unsaturated to saturated sterols *in vitro* has not been accomplished. Although it was believed that the transformation of cholesterol (XXII) into coprosterol (XXV) (the reduced form in which cholesterol is excreted by humans and carnivores) was effected by intestinal bacteria, this hydrogenation was not successful when attempted with bacterial cultures isolated from excrements.[84] The more recent work of Rosenheim and Webster[85] indicates that a specific dietetic factor rather than bacterial action may be responsible for this reduction. Since cholesterol is converted into cholestenone (XXIII) and coprostanone (XXIV) into coprosterol, an oxidation of the hydroxyl group probably occurs before hydrogenation; this was confirmed with the use of deuterium-containing material.[86] But it may still be shown that bacteria can carry out the reaction sequence. The catalytic hydrogenation of cholesterol yields exclusively dihydrocholesterol (XXVI) in which, in contrast to coprosterol, rings A and B are joined in the *trans* position.

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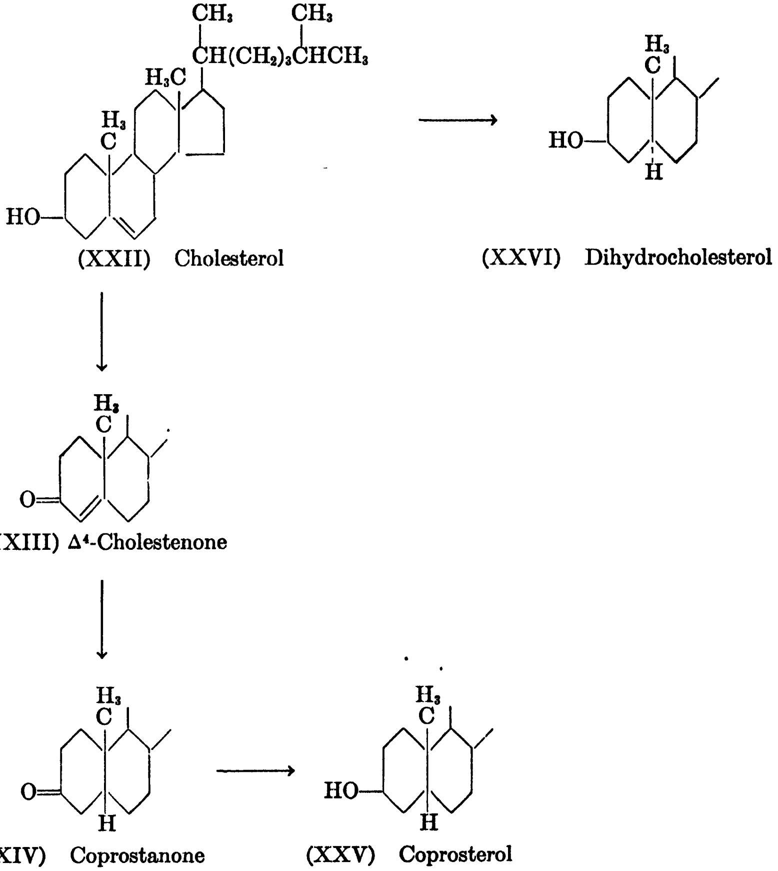
[82] Turfitt, *Biochem. J.*, 38, 492 (1944).

[83] Mamoli and Vercellone, *Ber.*, 70, 470 (1937).

[84] Schoenheimer, Behring, Hummel, and Schindel, *Z. physiol. Chem.*, 192, 73 (1930).

[85] Rosenheim and Webster, *Biochem. J.*, 35, 920, 928 (1941); 37, 589 (1943).



(XXII) Cholesterol

(XXVI) Dihydrocholesterol

(XXIII) Δ^4-Cholestenone

(XXIV) Coprostanone

(XXV) Coprosterol

The biological saturation of an ethylenic bond in the bile acids has not as yet been described, although in numerous investigations from the Physiological Chemical Institute in Okayama the reduction of the carbonyl group

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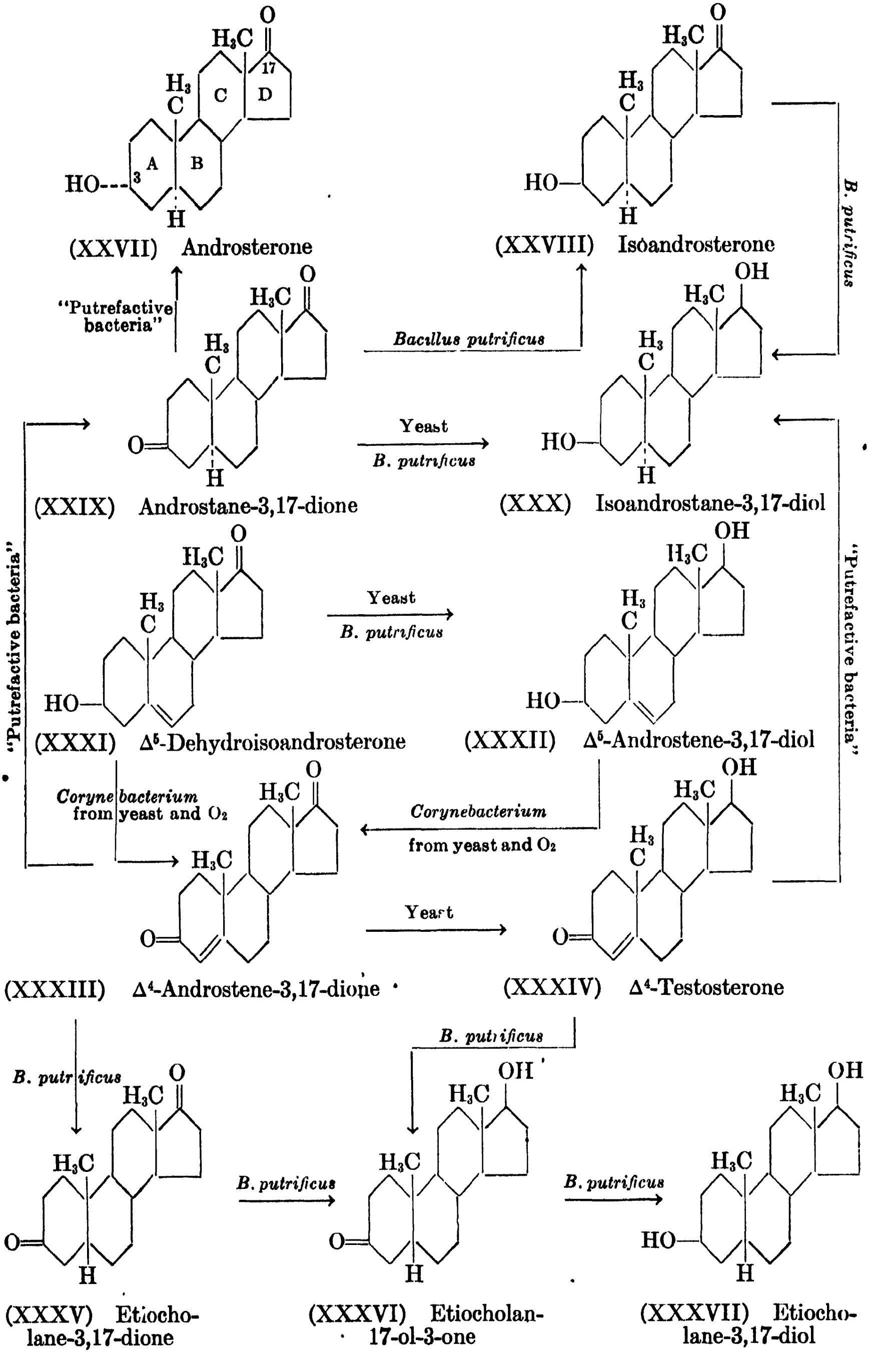
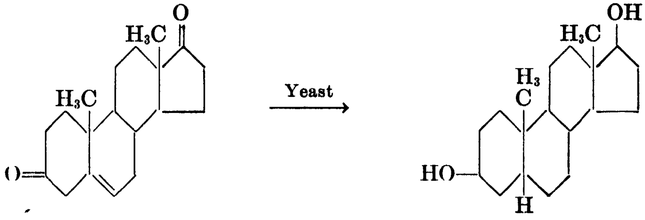
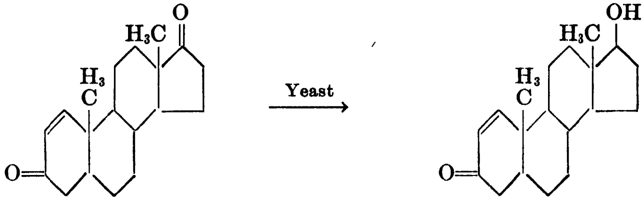
[86] Anchel and Schoenheimer, *J. Biol. Chem.*, **125**, 23 (1938); see also Enders, *Angew. Chem.*, **53**, 28 (1940).

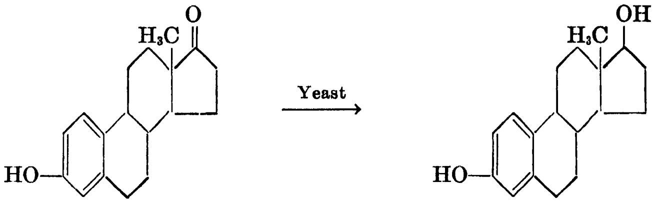

(XXVII) Androsterone
(XXVIII) Isoandrosterone
"Putrefactive bacteria"
Bacillus putrificus
B. putrificus
(XXIX) Androstane-3,17-dione
Yeast
B. putrificus
(XXX) Isoandrostane-3,17-diol
"Putrefactive bacteria"
"Putrefactive bacteria"
(XXXI) Δ⁵-Dehydroisoandrosterone
Yeast
B. putrificus
(XXXII) Δ⁵-Androstene-3,17-diol
Corynebacterium from yeast and O₂
Corynebacterium from yeast and O₂
(XXXIII) Δ⁴-Androstene-3,17-dione
Yeast
(XXXIV) Δ⁴-Testosterone
B. putrificus
B. putrificus
(XXXV) Etiocholane-3,17-dione
B. putrificus
(XXXVI) Etiocholan-17-ol-3-one
B. putrificus
(XXXVII) Etiocholane-3,17-diol
A
B
C
D
3
17



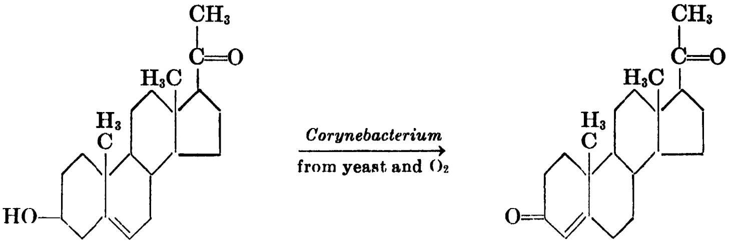
(XXXVIII) Δ^5-Androstene-3,17-dione (XXXIX) Isoandrostane-3,17-diol



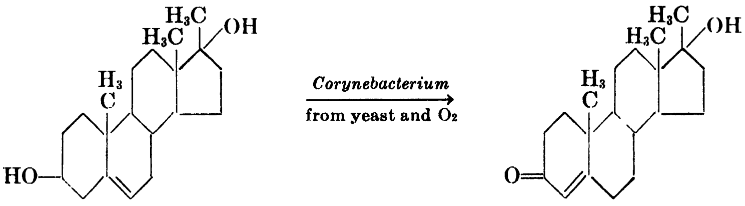
(XL) Δ^1-Androstene-3,17-dione (XLI) Δ^1-Androsten-17-ol-3-one



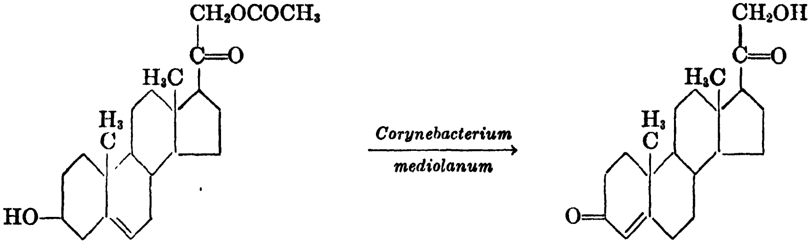
(XLII) Estrone (XLIII) Estradiol



(XLIV) Δ^5-Pregnen-3-ol-20-one (XLV) Progesterone



(XLVI) 17-Methyl-Δ^4-androstene-3,17-diol (XLVII) 17-Methyltestosterone



(XLVIII) Δ^5-Pregnen-3-ol-20-one 21-acetate (XLIX) Desoxycorticosterone

has been noted in different ketocholanic acids.[87] This research has been concerned with the problem of the hypothetical transformation of sterols into bile acids and the epimerization of the C_3 hydroxyl group which must occur. (See the formula for cholic acid (XXI).) These reductions, which have been carried out in the majority of cases with yeast, *E. coli*, or *B. proteus*, and with toads or rabbits as the experimental animals, are unlikely to be considered for preparative purposes.

Recent work has indicated that biological oxidations of bile acids may have some synthetic value. Schmidt *et al.*[88] reported the conversion of cholic acid into 3,7,12-triketocholanic acid in 85% yield by the action of *Alcaligenes faecalis.*

2. Steroid Hormones

In this group of compounds the possibilities of successful application of biochemical hydrogenation and dehydrogenation to synthetic work have undergone a thorough and successful treatment. Not only reductions of the carbonyl groups in ketonic sex hormones, but also dehydrogenations of hydroxyl groups have been carried out.

A. Reduction of Keto Steroids

The process of zymochemical reduction with yeast can be extended without essential technical modification to ketonic sex hormones. In one of the first of these reactions to be performed, Mamoli and Vercellone[89] obtained the alcohol Δ^5-androstene-3,17-diol (XXXII) in 20% yield from Δ^5-dehydroisoandrosterone (XXXI). The same treatment[90] of the unsaturated diketone Δ^4-androstene-3,17-dione (XXXIII) led solely to the reduction of the C_{17} carbonyl group with the formation of Δ^4-testosterone (XXXIV), the testicle hormone reported by Laqueur. The inability of the C_3 carbonyl group to add hydrogen probably is not attributable to its position in the molecule but rather to its conjugation with the double bond, since the saturated diketone androstane-3,17-dione (XXIX) when subjected to the same conditions of fermentation[91] yields 75% of isoandrostane-3,17-diol (XXX). Enzymic reduction of Δ^5-androstene-3,17-dione (XXXVIII) yields mainly isoandrostane-3,17-diol (XXXIX) together with a smaller quantity of Δ^4-testosterone (XXXIV).[92] The ethylenic bond β,γ to the C_3 carbonyl group does not hinder its reduction, but it is surprising that the ethylenic bond is saturated. The formation of the small amount of testosterone may be explained by the shifting of the double bond to the 4,5 position under the influence of enzyme action, whereupon the carbonyl group resists hydrogenation. It has been shown that the presence of a three-membered ring protects the adjacent carbonyl group at C_6 against hydrogenation by yeast in a manner similar to the protection given to a ketone group at C_3 by a C—C double bond conjugated with it at C_4. *i*-Androstane-6,17-dione yields about 50% of *i*-androstan-17-ol-6-one.[93]

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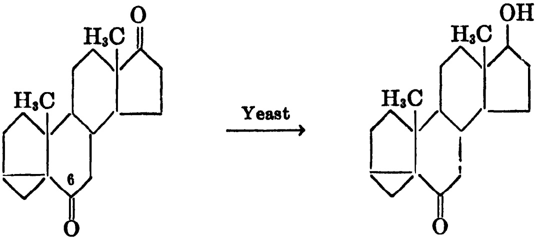
[87] Fischer, *Fortschritte der Chemie organischer Naturstoffe,* Vienna, 1939, Vol. III, p. 56. Tukamoto, *Z. physiol. chem.*, **260,** 210 (1939). Fukui, *J. Biochem.* (*Japan*), **25,** 61 (1936). Sihn, *ibid.*, **28,** 165 (1938). Mori, *ibid.*, **29,** 87 (1939). Miyazi, *Z. physiol. Chem.*, **254,** 104 (1938). Kim, *ibid.*, **255,** 267 (1938); *Enzymologia,* **6,** 105 (1939).

[88] Schmidt, Hughes, Green, and Cooper, *J. Biol. Chem.*, **145,** 229 (1942). Hoehn, Schmidt, and Hughes, *ibid.*, **152,** 59 (1944).

[89] Mamoli and Vercellone, *Z. physiol. Chem.*, **245,** 93 (1937).

[90] See footnote 83 and also French Patent, 843,071 (Schering A. G.), June 26, 1939 [*Chem. Abstracts,* **34,** 6413 (1940)]. Other patents relating to the yeast reduction of carbonyl groups in the 10,13-dimethylpolyhydrocyclopentanophenanthrene series are: U. S. Patent, 2,186,906 (Schering Corp.), January 9, 1940 [*Chem. Abstracts,* **34,** 3436 (1940)]; German Patent, 705,313 (Schering A. G.), March 20, 1941 [*Chem. Abstracts,* **36,** 2090 (1942)].



i-Androstane-6,17-dione *i*-Androstan-17-ol-6-one

The protecting action of an ethylenic bond conjugated with a carbonyl group is also shown by the fact that Δ^1-androsten-17-ol-3-one (XLI) is formed in 83% yield from Δ^1-androstene-3,17-dione (XL).[94] However, in an extension of this work Butenandt, Dannenberg, and Suranyi[95] showed that both Δ^1-androstene-3,17-dione (XL) and Δ^1-androsten-17-ol-3-one (XLI) can be reduced by fermenting yeast to isoandrostane-3,17-diol (XXX). Since Δ^1-cholestenone and Δ^1-allopregnene-3,20-dione are com-

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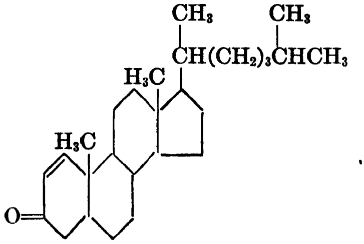
[91] Vercellone and Mamoli, *Z. physiol. Chem.*, **248**, 277 (1937).

[92] Mamoli and Vercellone, *Ber.*, **70**, 2079 (1937).

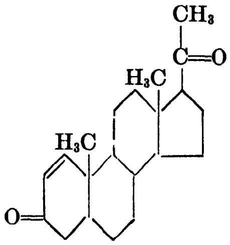
[93] Butenandt and Suranyi, *Ber.*, **75**, 591 (1942). For a short bibliography of work relating to pentacyclic steroids, see Rosenheim, *Nature*, **147**, 776 (1941).

[94] Butenandt, Dannenberg, Dresler, and Meinerts, *Ber.*, **71**, 1681 (1938).

[95] Butenandt, Dannenberg, and Suranyi, *Ber.*, **73**, 818 (1940).



Δ^1-Cholestenone



Δ^1-Allopregnene-3,20-dione

pletely resistant to fermenting yeast, it is apparent that Mamoli's rule, according to which a double bond in conjugation with a carbonyl group hinders its reduction in the action of fermenting yeast on steroids, must be modified. Evidently the structure of the side chain at C_{17} may be responsible for this stability of certain Δ^1-3-keto steroids.[95] In addition, the position in the molecule of the conjugated double bond is important: when there is no side chain as a determining factor, the carbonyl group is protected against reduction if the conjugated double bond is at the junction of rings A and B (for example at C_4).[93] The same phenomenon is also observed with simple α,β-unsaturated ketones such as pulegone or carvone whose double bond is attached to a tertiary carbon atom.

The zymochemical reduction of the C_{17} carbonyl group can be accomplished also in the group of estrogenic hormones: α-estradiol (XLIII), the physiologically active material in the Allen-Doisy test for estrogens, is formed from estrone (XLII). According to Mamoli,[96] estrone should be subjected to the action of yeast in the form of a low molecular weight fatty acid ester, since the free phenol is not satisfactorily hydrogenated under the conditions employed. However, Wettstein[97] was able to show that estrone itself can be converted in a short time to α-estradiol[98] in 70% yield. The formation of the 17-epimer, β-estradiol, seems to occur only in small quantity if at all.

REDUCTION OF ESTRONE TO α-ESTRADIOL BY YEAST.[97] A mixture of 200 g. of pure glucose, 100 g. of fresh pressed yeast, and 1.2 liters of tap water, contained in a closed flask equipped with a gas exit tube, is allowed to ferment for a short time at 37°C. with vigorous stirring, after the whole apparatus and reactants, without the yeast, had been carefully sterilized at 105°C. A solution of 1 g. of pure estrone in 50 ml. of freshly distilled dioxane is added dropwise and stirring continued for an additional 24 hours at 37°C. After each 24 hours of fermentation 100 g. of yeast, 200 g. of glucose, and 300 g. of water are added, and this addition is repeated four times, after which the whole is stirred for 42 hours.

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[96] Mamoli, *Ber.*, 71, 2696 (1938).

[97] Wettstein, *Helv. Chim. Acta*, 22, 250 (1939).

[98] See also British Patent, 511,433 (Schering Corp.), August 18, 1939 [*Chem. Abstracts*, 34, 6022 (1940)].

After thorough extraction of the reaction mixture with ether, the extract is washed first with water, then with saturated sodium bicarbonate solution, and finally water, and is evaporated; the residue is separated into ketonic and non-ketonic fractions by Girard's reagent. In this way about 300 mg. of estrone is recovered, and about 500 mg. of pure α-estradiol is obtained.

The reduction of the carbonyl group of keto steroids may be carried out by the action of putrefactive bacteria as well as by yeast. Testosterone (XXXIV) yields etiocholan-17-ol-3-one (XXXVI) by reduction of the double bond, and finally etiocholane-3,17-diol (XXXVII) after 20 days treatment with an unsterilized extract from stallion testicles.[99] In another experiment with intentionally putrefied extracts from bull testicles, isoandrostane-3,17-diol (XXX) was obtained from the testicle hormone in addition to etiocholanediol.[100] The reduction of androstane-3,17-dione (XXIX) with unidentified putrefactive bacteria produces, besides small quantities of diol, a mixture of both C_3 isomeric keto alcohols, isoandrosterone (XXVIII) and androsterone (XXVII), and consequently proceeds in both sterically possible directions.[100]

A pronounced stereochemical specificity of the reduction in relation to the configuration of the substrate has been established[101] by the use of a pure bacterial strain of *B. putrificus.* After inoculation with this strain, produced in a sterile yeast suspension as a nutrient medium for the bacteria, Δ^4-androstene-3,17-dione (XXXIII) adds hydrogen not only at the ethylenic bond but also at the carbonyl group to form etiocholan-17-ol-3-one (XXXVI) and etiocholane-3,17-diol (XXXVII). Under the same conditions, androstane-3,17-dione (XXIX) yields isoandrosterone (XXVIII) and isoandrostane-3,17-diol (XXX); testosterone (XXXIV) forms etiocholan-17-ol-3-one (XXXVI) and etiocholane-3,17-diol (XXXVII); Δ^5-dehydroisoandrosterone (XXXI) gives Δ^5-androstene-3,17-diol (XXXII) in good yield.

Apparently the androstenedione in which rings A and B are linked in the *cis* position is first converted to etiocholanedione; the C_{17} carbonyl of the reduced diketone is hydrogenated next so that the newly formed hydroxyl group is located in *trans* position to the methyl group at C_{18}. Finally the C_3 hydroxyl group resulting from the reduction of the corresponding carbonyl group forms in *trans* position to the C_{10} angular methyl group.

With the androstanedione which has a *trans* linkage of rings A and

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[99] Ercoli, *Ber.*, **71**, 650 (1938).

[100] Mamoli and Schramm, *Ber.*, **71**, 2698 (1938).

[101] Mamoli, Koch, and Teschen, *Z. physiol. Chem.*, **261**, 287 (1939).

B, bacterial reduction proceeds in a different manner; in this case the C_3 carbonyl group is first reduced, forming a hydroxyl group which is in *cis* position to the C_{13} methyl group. Since isoandrosterone is the compound formed from this hydrogenation, the *cis* configuration is established. The reduction of the C_{17} carbonyl group which then follows yields a hydroxyl group with the same steric orientation.

REDUCTION OF ANDROSTENE-3,17-DIONE TO ETIOCHOLAN-17-OL-3-ONE AND ETIOCHOLANE-3,17-DIOL.[101] A suspension of 10 g. of bakers' yeast in 60 ml. of tap water is buffered with 10 ml. of 0.2 *M* disodium hydrogen phosphate and 10 ml. of 0.2 *M* potassium dihydrogen phosphate (pH 6.8), mixed with 150 mg. of finely pulverized androstenedione, and sterilized 1 hour in an autoclave. After cooling, the mixture is inoculated with several drops of a pure freshly cultivated *B. putrificus* strain and is shaken under nitrogen for 6 days at 36° to 37°C. At the end of this time the reaction mixture (pH 6.6) is exhaustively extracted with ether. After washing, drying, and evaporating the ether solution, the ketone and alcohol portions in the resulting residue are separated by means of Girard's Reagent T. In this way 20 mg. of etiocholane-3,17-diol and 60 mg. of etiocholan-17-ol-3-one are obtained.

B. Dehydrogenation of Hydroxy Steroids

Vercellone and Mamoli,[102] who observed the dehydrogenation of Δ^5-androstene-3,17-diol (XXXII) to Δ^4-androstene-3,17-dione (XXXIII) after shaking for 2 days under oxygen with yeast whose activity had been reduced, concluded that the reaction was caused by yeast fermentation; but Schramm and Mamoli[103] showed that aerobic bacteria, which could be obtained from Milan yeast and grown in yeast water, were responsible for this action. Ercoli[104] has transformed Δ^5-androstane-3,17-diol (XXXII) into testosterone (XXXIV) (64%) and Δ^4-androstene-3,17-dione (XXXIII) (4%) by the use of *Micrococcus dehydrogenans*[105] from pressed yeast.

Δ^5-Dehydroisoandrosterone (XXXI) is converted to Δ^4-androstene-3,17-dione (XXXIII) in excellent yield.[106] This dehydrogenation goes so smoothly that isolation of the diketone is not necessary when a partial reduction to testosterone (XXXIV) is intended. The yield of testosterone from dehydroisoandrosterone is about 80%.[107]

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[102] Vercellone and Mamoli, *Ber.*, **71**, 152 (1938).

[103] Schramm and Mamoli, *Ber.*, **71**, 1322 (1938).

[104] Ercoli, *Z. physiol. Chem.*, **270**, 266 (1941).

[105] This same microorganism has been used in other transformations of this type; see Ercoli, *Biochim. terap. sper.*, **28**, 125 (1941) [*Chem. Abstracts*, **38**, 2987 (1944)].

[106] Mamoli and Vercellone, *Ber.*, **71**, 1686 (1938). Almost quantitative yields are also obtained with *Micrococcus dehydrogenans*; see Ercoli, *Boll. sci. facoltà chim. ind. Bologna*, **1940**, 279 [*Chem. Abstracts*, **38**, 1540 (1944)].

[107] Mamoli, *Ber.*, **71**, 2278 (1938). See also U. S. Patent, 2,236,574 (Schering Corp.), April 1, 1941 [*Chem. Abstracts*, **35**, 4393 (1941)].

With the bacteria from Milan yeast, the dehydrogenation of the C_3 hydroxyl group of Δ^5-pregnen-3-ol-20-one (XLIV) takes place to form the corpus luteum hormone progesterone (XLV) in 40% yield, while cholesterol is wholly unchanged under the same conditions.[108] 17-Methyl-Δ^4-androstene-3,17-diol (XLVI) can be transformed to 17-methyltestosterone (XLIX) in 75% yield.[109]

Later, Mamoli, Koch, and Teschen[110] succeeded in cultivating a pure bacterial strain. Its properties of dehydrogenating secondary steroid alcohols were found to agree with those described in the literature for *Corynebacterium helvolum* (Lehmann and Neumann). The new bacterium was named *Corynebacterium mediolanum* to indicate its origin.

With the latter bacterium, Δ^5-pregnen-3-ol-20-one 21-acetate (XLVIII), a cortical steroid, can be converted with simultaneous saponification of the acetoxy group in 34% yield to desoxycorticosterone (Δ^4-pregnen-21-ol-3,20-dione) (XLIX), the physiologically most active substance in the adrenal group.[111] Although a primary hydroxyl group is formed at C_{21} during the treatment, it is not oxidized.

OXIDATION OF ACETOXYPREGNENOLONE TO DESOXYCORTICOSTERONE.[111] Sterile yeast water (60 ml.) buffered by the addition of 10 ml. of 0.2 *M* disodium hydrogen phosphate and 10 ml. of 0.2 *M* potassium dihydrogen phosphate is treated with 200 mg. of finely pulverized 21-acetoxypregnen-3-ol-20-one and sterilized 1 hour in an autoclave. After cooling, it is inoculated with several drops of a fresh culture of *C. mediolanum*. The reaction mixture is then shaken at 36° to 37°C. under oxygen for 6 days. At the end of that time, the suspension is filtered, the residue taken up with acetone, freed from bacteria by filtration, and the acetone evaporated. The residue from this treatment is recrystallized carefully from dilute acetone. The first crop consists of 54 mg. of starting material. After the mother liquor has been evaporated to dryness and the residue dissolved in a little acetone and treated with ether, 48 mg. of desoxycorticosterone, m.p. 139° to 140°C. (uncorrected) (identified by mixed m.p. with an authentic sample), is obtained. From the residual mother liquor, 12 mg. more of the same product is secured by distillation in a high vacuum.

Those cases in which bacterial dehydrogenation of sterols offers definite advantages over the purely chemical processes which are known to be applicable in the chemistry of the steroids will not be discussed in detail in this section. The Oppenauer oxidation, which is an exchange of oxidation stages between alcohols and ketones in the presence of aluminum alkoxides or aluminum phenoxide, has proved valuable in steroid transformations.[112] This oxidation has recently undergone a very interesting modification by Wettstein.[113] By the use of benzoquinone as the hydrogen acceptor, Δ^5-3-hydroxy steroids can be converted to $\Delta^{4,6}$-3-keto steroids, thus simultaneously introducing a second double bond.

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[108] Mamoli, *Ber.*, **71**, 2701 (1938). Good yields of progesterone are obtained by the use of *Micrococcus dehydrogenans*; see Ercoli, *Boll. sci. facoltà chim. ind. Bologna*, **1940**, 279 [*Chem. Abstracts*, **38**, 1540 (1944)].

[109] Mamoli, *Gazz. chim. ital.*, **69**, 237 (1939).

[110] Mamoli, Koch, and Teschen, *Naturwissenschaften*, **27**, 319 (1939).

[111] Mamoli, *Ber.*, **72**, 1863 (1939).

C. Hydrogenation of Unsaturated Steroids

Saturation of the ethylenic bond in steroids by bacteria has been established by examination of the action of enzymes. By allowing Δ^4-androstene-3,17-dione (XXXIII) to stand 20 days with an extract from stallion testicles, Ercoli and Mamoli[114] showed that etiocholane-3,17-dione (XXXV) was formed. With the same extract from bull testicles Ercoli[99] transformed testosterone (XXXIV) in 10 days to etiocholan-17-ol-3-one (XXXVI) and further in 20 days to etiocholane-3,17-diol (XXXVII). This latter substance may also be isolated from male urine.

Ercoli's assumption that the addition of hydrogen may be traced to a "testis hydrogenase" has now been disproved. Schramm and Mamoli[103] were able to show that these hydrogenations of unsaturated male hormones occur through bacterial action. Testicle extracts do not bring about hydrogenation if sterilized by heat and kept sterile. But after inoculation of the boiled extract with putrefactive bacteria, the addition of hydrogen to Δ^4-androstene-3,17-dione or to testosterone may be accomplished with the formation of etiocholane-3,17-diol.[115] In another investigation,[100] isoandrostane-3,17-diol (XXX) was identified in addition to an approximately equal quantity of etiocholane-3,17-diol which had previously been the only product isolated. In this case the hydrogenation of the double bond leads both to the *cis*-etiocholane series, and to the *trans*-androstane series. This formation of different steric isomers may be accounted for by variations in the composition of the bacterial mixture occurring through accidental contamination.

Hydrogenations with a pure bacterial strain (which is probably identical with the Beinstock *Bacillus putrificus*) isolated from putrescent bull testicle extract show a remarkable stereochemical specificity.[116]

Powdered Δ^4-androstene-3,17-dione (XXXIII) in sterile neutral buffered yeast water, after being inoculated with *B. putrificus* and shaken for 6 days at 37°C. under nitrogen, produced only etiocholane-3,17-dione

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[112] Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937). See also Inhoffen, Logemann, Hohlweg, and Serini, *Ber.*, **71**, 1032 (1938).

[113] Wettstein, *Helv. Chim. Acta*, **23**, 389 (1940).

[114] Ercoli and Mamoli, *Ber.*, **71**, 156 (1938).

[115] Mamoli and Schramm, *Ber.*, **71**, 2083 (1938).

[116] Mamoli, Koch, and Teschen, *Z. physiol. Chem.*, **261**, 287 (1939).

(XXXV) in 70 to 80% yield. In the same way, testosterone (XXXIV) is transformed into etiocholan-17-ol-3-one (XXXVI) (70 to 80%) and the pregnancy hormone progesterone (XLV) into pregnanedione in 80 to 90% yield.

Thus in yeast water the bacterial hydrogenation stops after saturation of the double bond; and with this addition of hydrogen, there results exclusively a *cis* linkage of rings A and B (cholanic acid series). Since catalytic hydrogenation does not proceed satisfactorily in this series the biochemical method possesses great advantage in the cases mentioned above.

If a sterile yeast suspension is used as nutrient medium for the bacteria instead of yeast water, hydrogenation of the double bonds and of the ketone groups takes place, as with androstenedione and testosterone. This has been explained in the preceding section.

REDUCTION OF ANDROSTENEDIONE TO ETIOCHOLANEDIONE.[116] Finely powdered androstenedione (150 mg.) is added to 60 ml. of sterile yeast water buffered by 10 ml. of 0.2 *M* disodium hydrogen phosphate and 10 ml. of 0.2 *M* potassium dihydrogen phosphate to a pH of 6.8 and the mixture is sterilized 1 hour in an autoclave. After cooling, it is inoculated with several drops of a culture of a pure strain of *B. putrificus*, freshly grown in yeast mash. The reaction mixture is then shaken at 36° to 37°C. under nitrogen for 6 days. At the end of this time the suspension is filtered (pH 6.6), and the residue boiled with acetone and freed from the bacilli by filtering. The acetone solution is evaporated to dryness and the residue recrystallized from dilute methanol and dilute acetone. In this way 115 mg. of etiocholanedione, m.p. 130° to 131°C. (uncorrected) (identified by mixed m.p. with an authentic sample), is obtained.

Various transformations in the steroid series involving oxidation of hydroxyl groups and reduction of ketone groups and ethylenic bonds have been carried out in the animal organism. In general several products are obtained, and, since the yields have been poor, these reactions are not as yet used for preparative purposes.[117] A few typical examples may be mentioned: α-estradiol has been converted into estrone[118,119]; testosterone into androsten-17-one, androsterone, and etiocholan-3-ol-17-one[120]; and progesterone[121] and desoxycorticosterone[122] into pregnanediol. Reductions of ethylenic bonds and carbonyl groups have also been carried out with certain sapogenins.[123]

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[117] If water-insoluble materials are excreted in the urine of experimental animals these substances are often conjugated with glucuronic acid; see Munson, Gallagher, and Koch, *J. Biol. Chem.*, **152**, 67 (1944). Since considerable advances have been made in methods of separating steroids from urine, it is possible that certain transformations in the animal body may be shown to have preparative value; see Venning, Hoffman, and Browne, *J. Biol. Chem.*, **146**, 369 (1942); Gallagher, Munson, and Koch, *Endocrinology*, **30**, 1036 (1942); Talbot, Ryan, and Wolfe, *J. Biol. Chem.*, **148**, 593 (1943); **151**, 607 (1943).

[118] Heard, Bauld, and Hoffman, *J. Biol. Chem.*, **141**, 709 (1941).

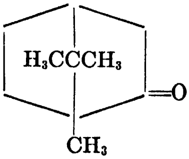
[119] Dorfman, Wise, and van Wagenen, *Endocrinology*, **36**, 347 (1945).

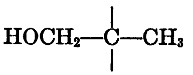
[120] Fish and Dorfman, *Endocrinology*, **35**, 22 (1944).

VII. OXIDATION OF METHYL GROUPS

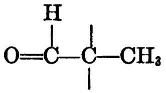
1. General Considerations

The preferential oxidation in the animal organism of branched or terminal methyl groups in many different substances has been observed over a period of years.[124] Thus, for example, dogs excrete antipyrine in part as hydroxyantipyrine glucuronide.[125] With *n*-alkylbenzenes the oxidation very probably starts first at the end of the side chain.[126] The so-called camphorol, a mixture of hydroxy derivatives, is formed in the animal body from camphor (L), and is isolated from the urine as the glucuronide. Besides this mixture containing 3- and 5-*cis*-π- and *trans*-π-hydroxycamphor (La), *trans*-π-ketocamphor (Lb) (which is responsible for the restorative action of camphor) and the corresponding acid, *trans*-π-apocamphor-7-carboxylic acid (Lc), have been detected as oxidation products.[127]

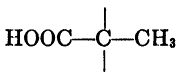

(L)


$\mathrm{HOCH_2{-}\overset{|}{\underset{|}{C}}{-}CH_3}$

(La)

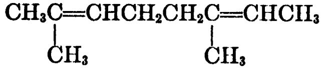

$\mathrm{O{=}\overset{H}{\overset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}CH_3}$

(Lb)

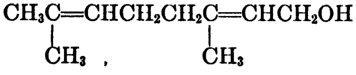

$\mathrm{HOOC{-}\overset{|}{\underset{|}{C}}{-}CH_3}$

(Lc)

With some fatty acids containing an uneven number of carbon atoms, evidently ω-oxidation of the methyl group occurs as well as oxidation at the carboxyl end of the molecule, since dicarboxylic acids with the same number of carbon atoms can be isolated.[128]


$\mathrm{CH_3\underset{CH_3}{\underset{|}{C}}{=}CHCH_2CH_2\underset{CH_3}{\underset{|}{C}}{=}CHCH_3}$

(LI) Dihydromyrcene


$\mathrm{CH_3\underset{CH_3}{\underset{|}{C}}{=}CHCH_2CH_2\underset{CH_3}{\underset{|}{C}}{=}CHCH_2OH}$

(LIa) Geraniol

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[121] Westphal, *Z. physiol. Chem.*, **273**, 1 (1942).

[122] Westphal, *Z. physiol. Chem.*, **273**, 13 (1942). Hoffman, Kazmin, and Browne, *J. Biol. Chem.*, **147**, 259 (1943). Horwitt, Dorfman, Shipley, and Fish, *ibid.*, **155**, 213 (1944). Fish, Horwitt, and Dorfman, *Science*, **97**, 227 (1943).

[123] Marker, Wittbecker, Wagner, and Turner, *J. Am. Chem. Soc.*, **64**, 818 (1942). Marker, Wagner, and Ulshafer, *ibid.*, **64**, 1653 (1942).

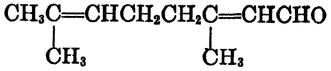
[124] Fromherz, *Bethes Handbuch der normalen und pathologischen Physiologie*, Springer Berlin, 1939, Vol. V, p. 996.

[125] Lawrow, *Ber.*, **33**, 2344 (1900); *Z. physiol. Chem.*, **32**, 111 (1901).

[126] Thierfelder and Klenk, *Z. physiol. Chem.*, **141**, 13, 29 (1924).

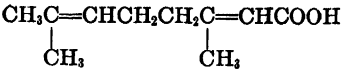
[127] Asahina and Ishidate, *Ber.*, **61**, 533 (1928); **68**, 947 (1935).

[128] Verkade, Elzas, van der Lee, Wolff, Verkade-Sandbergen, and van der Sande, *Z. physiol. Chem.*, **215**, 225 (1933).



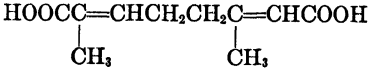
$CH_3\underset{CH_3}{C}=CHCH_2CH_2\underset{CH_3}{C}=CHCHO$

(LIb) Citral



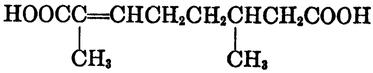
$CH_3\underset{CH_3}{C}=CHCH_2CH_2\underset{CH_3}{C}=CHCOOH$

(LIc) Geranic acid



$HOOC\underset{CH_3}{C}=CHCH_2CH_2\underset{CH_3}{C}=CHCOOH$

(LId) Hildebrandt's acid



$HOOC\underset{CH_3}{C}=CHCH_2CH_2\underset{CH_3}{C}HCH_2COOH$

(LIe) Dihydro-Hildebrandt's acid

Geraniol (LIa), citral (LIb), and geranic acid (LIc) were likewise isolated in part as dicarboxylic acids with an undiminished number of carbon atoms.[129] With further investigation of the latter transformation, including additional substances with branched methyl groups, it became evident that the preferential oxidation of methyl groups is a general reaction.[80] Thus dihydromyrcene (LI) yields the same dicarboxylic acid, $C_{10}H_{14}O_8$, as the previously mentioned aliphatic terpenes. This dicarboxylic acid, which results from geraniol, citral, and geranic acid in about 10% yield, is Hildebrandt's acid (LId). Moreover, a dihydro acid (LIe) is formed in larger quantity by hydrogenating the α,β double bond of geraniol.

This biological oxidation of methyl groups may prove valuable in certain syntheses, especially of compounds whose oxidative decomposition is made more difficult by branching of the carbon chain β to the hydroxyl or carbonyl group.

2. General Experimental Procedure

Undiluted liquid compounds have been administered via a stomach tube to rabbits which may serve as experimental animals; two 5 g. injections are given a day per animal. Such liquids in quantities of 3 to 6 ml. can also be injected alternately in the muscles of the right and left thigh. Solid substances can be dissolved in olive oil and then emulsified with water, or simply finely powdered and suspended in water. Before dispersion, acids are transformed into their salts by accurate neutralization with the calculated quantity of sodium hydroxide. In some cases they can also be administered as the methyl esters.

The urine is collected from the metabolism cages daily during the feeding and also for 2 or more additional days, and preserved against putrefaction by the addition of a little chloroform. If air-sensitive materials are present, the urine is best stored under nitrogen in a brown bottle in the refrigerator. The desired material is obtained by exhaustive ether extraction of the urine after splitting the conjugated compounds; and acids are isolated by precipitating their lead salts.

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[129] Hildebrandt, *Arch. exp. Path. Pharmakol.*, **45**, 110 (1901).

The following treatment is used for obtaining the acid products from geraniol.[80] A saturated solution of barium hydroxide is added to the urine until a precipitate separates; the mixture is heated to boiling, filtered, and the precipitate washed with hot water. After lead acetate is added to the filtrate until no more precipitate forms, the lead precipitate is filtered cold, washed with cold water, and decomposed in the cold with hydrogen sulfide. The lead sulfide precipitate is boiled three or four times with water and the resulting solutions are concentrated together with the first filtrate. Most of the Hildebrandt's acid separates as white clusters of needles; only a small portion is found in the dark brown oil deposited. The dihydro-Hildebrandt's acid can be isolated from this oil by taking it up in ether, evaporating the solvent, and decolorizing an aqueous solution of the residue with charcoal. The total yield of the two acids is 27%.

To obtain all the ether-soluble substances in the urine[130] and to distinguish the conjugated and unconjugated fractions, the strongly alkaline reacting urine is extracted with ether. After acidification to Congo red with sulfuric acid, the reaction mixture is boiled 20 minutes and is again extracted thoroughly with ether. The acids are removed from both ether extracts with dilute sodium hydroxide, and the neutral fractions are obtained after washing, drying, and evaporating. Further purification is achieved by distillation in a high vacuum.

VIII. CONCLUSION

In the article[131] printed a century ago in Liebig's *Annalen* entitled *Das enträtselte Geheimnis der geistigen Gährung* S. Windler (Wöhler) describes how brewers' yeast develops into small animals which have the form of a Beindorf distilling vessel without the cooling apparatus. They eat sugar by means of probosces which are studded with bristles, and secrete alcohol from the intestinal tract and carbon dioxide from the urinary organs. The satire refers to the microscopic observations of Schwann and Cagniard de Latour.

Liebig's mechanistic interpretation and the vitalistic theory were merged long ago. Today the chemist does not doubt that microorganisms, as was suggested in this "Joke about Fermentation,"[132] can be used as chemical factories for carrying out specific transformations, and he anticipates the discovery of new possibilities through further investigation of enzyme systems and of the metabolism of microorganisms.

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[130] Fischer and Bielig, *Z. physiol. Chem.*, **266**, 73 (1940). Bielig, Dissertation, Würzburg, 1939.

[131] S. Windler (Wöhler), *Ann.*, **29**, 100 (1839).

[132] Liebig, letter to Wöhler dated November 18, 1838.

Substitution Reactions of Aliphatic Compounds

By JOHANNES NELLES

Translated and revised by G. BRYANT BACHMAN

I. INTRODUCTION

The development of adequate synthetic methods in aliphatic chemistry was for long neglected in both university and industrial laboratories. There are various reasons for this. In the first place, aliphatic hydrocarbons are known to be relatively unreactive. They are resistant to the nitration, sulfonation, and Friedel-Crafts reactions so characteristic of aromatic compounds. In the second place, the isomeric relationships of products formed in substitution reactions are often much more complex for aliphatic compounds than for aromatic compounds. This has hindered the development of aliphatic chemistry. In the third place, there was once little technological interest in the chemistry of aliphatic compounds. In Germany, especially, the relative abundance of coal as compared to petroleum led to the careful examination of coal as a raw material. The synthesis from its aromatic constituents of various kinds of dyes and other products has proved of great value.

These factors have been changed materially during the past 20 years. Thus the proverbial chemical resistance of paraffins has been overcome by the application of modern experimental methods and the use of modern equipment. Technical interest has increased as a result of the development of the chemistry of petroleum, synthetic rubber, and catalytic aromatization, and through the preparation from aliphatic compounds of textile aids, and of vinyl and condensation polymers.

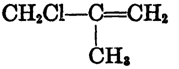
These developments have naturally led to an increase in the number of available synthetic methods in aliphatic chemistry. It may be said without exaggeration that in recent years procedures have been discovered which are the equal in elegance and simplicity of the long known aromatic reactions. This is especially true of catalytic processes. Their further development and their theoretical clarification are among the chief concerns of the future. With their aid many problems of aliphatic chemistry will be solved. Further advances in the methods of aliphatic chemistry, arrived at through the close collaboration of scientists and technologists, will provide the means for achieving these solutions.

In what follows there will be given a summary of the newer substitution reactions useful in the aliphatic series. The basic methods with general applicability will be considered, while procedures of value only in special cases will be omitted. Because of the great number of interesting methods developed in recent years, it has not been possible to make a complete literature survey of individual reactions. In many cases only the original article, or such publications as contain good bibliographies, will be cited.

II. HALOGENATION

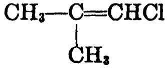
A series of publications and patents presenting new view-points and new experimental methods has appeared in the field of aliphatic halogen compounds in recent years. Although these methods require further development and application, they will be mentioned in this review because of the great technical importance of halogen compounds as starting materials for organic syntheses.

The substitutive chlorination of olefins in such a manner as to avoid saturation of the double bond dates back to the classical work of Sheshukov.[1] He observed that the action of halogen on isobutylene under the usual conditions leads to little or no addition product of the halogen to the double bond. Instead there is formed a mixture of isobutenyl chlorides consisting chiefly of I and II. After further work along these lines Kondakov[2] stated that those olefins which combine readily with mineral acids are converted by chlorine to monochloroolefins, while those unsaturated hydrocarbons which do not react readily with mineral acids add chlorine to the double bond. Recently these observations have been extended by Burgin, Engs, Groll, and Hearne[3] and by Schales[4] with the aid of modern physicochemical concepts and techniques. These investigations were concerned almost exclusively with branched chain olefins in which the double bond was located on a tertiary carbon atom.



$\mathrm{CH_2Cl{-}\underset{\underset{CH_3}{|}}{C}{=}CH_2}$

(I)



$\mathrm{CH_3{-}\underset{\underset{CH_3}{|}}{C}{=}CHCl}$

(II)

The introduction of halogen into straight chain olefins, such as ethylene, propylene, and butylene, without saturation of the double bond, was described first in patents[5] and later in a publication[6] of Groll and Hearne.

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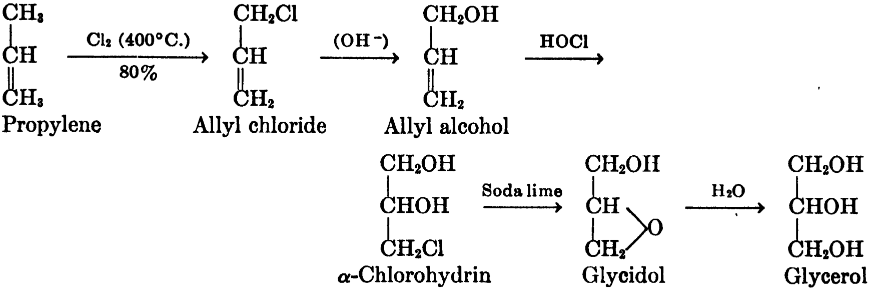
[1] *Ber.*, 17, 412 (1884).
[2] *Ber.*, 24, 929 (1891).
[3] *Ind. Eng. Chem.*, 31, 1413 (1939).
[4] *Ber.*, 70, 116 (1937).
[5] British Patent, 468,016; U. S. Patents, 2,077,382 and 2,130,084.
[6] *Ind. Eng. Chem.*, 31, 1530 (1939).

These investigators succeeded in converting ethylene to vinyl chloride and propylene to allyl chloride through chlorination in the gas phase at elevated temperatures (usually 200° to 600°C.). Thus, preheated propylene and chlorine were brought together at 600°C. in a suitable reactor and in the absence of a catalyst. The propylene was 82% converted to allyl chloride and less than 1% to dichloropropane. Allyl bromide was similarly obtained in 65% yield from propylene and bromine. Suitable reaction conditions and equipment were used to prevent explosions and to avoid corrosion. Apparently light and catalysts serve only to increase the rate of chlorination of straight chain olefins. None of the conditions investigated (temperature, phase, surface, impurities) alters the ratio of substitution isomers formed, although some of them influence the ratio of substitution products to addition products. Higher yields of substitution products are obtained at higher temperatures, the optimum range being at 300° to 600°C. Substitutive reactivity increases from ethylene through propylene, 2-butene, 2-pentene to isobutylene and other tertiary olefins. In general, excess olefin increases the amount of substitution, while excess chlorine has the reverse effect. The reaction was applied to the lower members of the olefin series only. Whether it can be used satisfactorily with higher molecular weight olefins and other unsaturated compounds is not known.

This new method of chlorination of hydrocarbons at high temperatures will eventually make available a series of theoretically and technically important substances. Halogen-containing olefins are capable of many interesting transformations. Thus glycerol may be obtained from propylene by way of allyl chloride.[7]



The direct action of halogens on hydrocarbons usually leads to a mixture of products halogenated to varying degrees. The preparation of monohalogen compounds by direct halogenation is not always easy. A familiar method is by the addition of hydrogen halide to olefins. This old procedure has recently been extended and improved by working in the gas phase and by employing various catalysts of the metal halide type, such as $AlCl_3$, $FeCl_3$, $ZnCl_2$, $AlBr_3$, etc. A useful method for the preparation of ethyl chloride or ethyl bromide from ethylene and hydrogen chloride or hydrogen bromide, with $AlCl_3$ or $AlBr_3$ as catalyst, is described by Tulleners, Tuyn, and Waterman.[8] Propylene and hydrogen chloride do not react in the gas phase in the absence of a catalyst. However, Brouwer and Wibaut[9] have shown that $FeCl_3$, $BiCl_3$, and $ZnCl_2$ on silica gel are good catalysts at room temperature, while $HgCl_2$, $NiCl_2$, $AlCl_3$, and $CaCl_2$ are better at higher temperatures. The reaction products are isopropyl chloride and a little polymer; no *n*-propyl chloride is formed.

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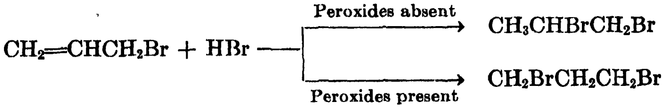
[7] *Ind. Eng. Chem., News Ed.*, **16**, 630 (1938).

According to Markovnikov the addition of hydrogen halides to olefins proceeds in such a manner that the halogen atom becomes attached to the carbon atom bearing the fewest hydrogen atoms. Recently, however, it has been observed that certain substances cause the addition of hydrogen bromide to many olefins to occur in the reverse senes. This is referred to as the *peroxide effect.*[10]

Kharasch[11] and his co-workers, in a series of investigations, found that the addition of hydrogen bromide to allyl bromide in the absence of peroxides proceeds according to Markovnikov's rule and gives 1,2-dibromopropane. In the presence of peroxides the reaction is faster and 1,3-dibromopropane is formed almost exclusively. Similar results were observed with vinyl bromide[12] and vinyl chloride.[13] In the presence of peroxides 1,2-dihalides are formed, while in the absence of oxygen or in the presence of antioxidants 1,1-dihalides are obtained.[14]



$$CH_2{=}CHCH_2Br + HBr \begin{cases} \xrightarrow{\text{Peroxides absent}} CH_3CHBrCH_2Br \\ \xrightarrow[\text{Peroxides present}]{} CH_2BrCH_2CH_2Br \end{cases}$$

Propylene and hydrogen bromide react normally to form isopropyl bromide. In the presence of benzoyl peroxide the reaction yields *n*-propyl bromide almost quantitatively.[15] The addition of hydrogen chloride to propylene is, on the other hand, not influenced by peroxides.[16] These investigations have also been extended to include higher olefins such as isobutylene, 1-pentene, and 1-heptene.[17]

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[8] *Rec. trav. chim.*, **53**, 544 (1934).

[9] *Rec. trav. chim.*, **53**, 1001 (1934).

[10] Smith, *Chemistry & Industry*, **56**, 833 (1937); *Ann. Repts. Progress Chem.*, **36**, 186 (1940). Mayo and Walling, *Chem. Revs.*, **27**, 351 (1940).

[11] *J. Am. Chem. Soc.*, **55**, 2468 (1933).

[12] *J. Am. Chem. Soc.*, **55**, 2521 (1933).

[13] *J. Am. Chem. Soc.*, **56**, 712 (1934).

[14] See also Kharasch *et al.*, *J. Org. Chem.*, **4**, 428 (1939).

[15] Kharasch *et al.*, *J. Am. Chem. Soc.*, **55**, 2531 (1933).

[16] Brouwer and Wibaut, *Rec. trav. chim.*, **53**, 1003 (1934).

[17] Sherrill, Mayer, and Walker, *J. Am. Chem. Soc.*, **56**, 926 (1934).

The action of peroxides in the addition of hydrogen bromide is not limited to compounds containing double bonds. It was shown by W. Bauer that addition to acetylene in the presence of oxidizing gases yields 1,2-dibromoethane.[18] Similarly 2-butyne yields 2,3-dibromobutane in the presence of peroxides.[19] Without such catalysts and with oxygen excluded 2,2-dibromobutane is formed.

It is evident that this new method is of great importance in preparing isomers heretofore not readily available. Although *abnormal* additions of all hydrogen halides are not observed, it is most helpful that controlled addition of hydrogen bromide may be achieved with peroxides as catalysts. It would appear that the effects caused by peroxides arise from their ability to initiate chain reactions in which atoms or free radicals act as chain carriers. The abnormal orientation observed probably depends on a change in the mechanism of addition from the normal electron-sharing type to an electron-pairing type.[20]

The peroxide effect is not limited to hydrogen bromide addition reactions. Mercaptans resemble hydrogen bromide in their response to peroxides and the addition of bisulfites to olefins is strongly inhibited in the absence of oxygen or peroxides. The orientation of addition of the molecules of both mercaptans and bisulfites may be a further indication of the peroxide effect:

$$\mathrm{RCH{=}CH_2 + R'SH \xrightarrow{\text{Peroxides}} RCH_2CH_2SR'}$$

$$\mathrm{RCH{=}CH_2 + NaHSO_3 \xrightarrow{\text{Peroxides}} RCH_2CH_2SO_3Na}$$

Kharasch and co-workers have published data on the influence of peroxides on the addition of bisulfite[21] and thioglycolic acid[22] to unsaturated compounds. Furthermore Kharasch and Brown[23] have found that traces of peroxides catalyze the chlorination of hydrocarbons by sulfuryl chloride. This method of chlorination possesses certain advantages over chlorination activated by light. It is difficult to substitute a second hydrogen by chlorine and a third hydrogen is not replaced. The method is especially valuable for introducing one aliphatic halogen atom into an alkyl group of dialkylbenzenes. Thus *m*-xylene yields only *m*-xylyl chloride. Aliphatic acids and their chlorides are readily chlorinated by this same process. The work of Bockemüller and Pfeuffer on peroxide formation during the bromination of olefins is a closely related phenomenon.[24]

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[18] German Patent 394,194.

[19] Walling, Kharasch, and Mayo, *J. Am. Chem. Soc.*, **61**, 1711 (1939).

[20] Remick, *Electronic Interpretations of Organic Chemistry*, Wiley, New York, 1943, p. 273.

[21] *Chemistry & Industry*, **57**, 774 (1938); *J. Am. Chem. Soc.*, **61**, 3092 (1939).

[22] *Chemistry & Industry*, **57**, 752 (1938).

[23] *J. Am. Chem. Soc.*, **61**, 2142, 3432 (1939); **62**, 925 (1940).

[24] *Ann.*, **537**, 178 (1939).

McBee, Hass, and co-workers[25] have introduced the term *chlorinolysis* to describe reactions they have studied which lead to carbon-carbon bond rupture during chlorination. They propose an economical synthesis of CCl_4 and C_2Cl_6 by chlorinolysis of petroleum hydrocarbons. Recent progress in chlorination has been reviewed by these authors.[26]

Fluorine compounds have found a number of technical applications in recent years including their use as refrigerants, aerosol dispersants, polymers, solvents, and intermediates.

The direct fluorination of organic compounds is not yet feasible commercially, because the process is not subject to proper control. Laboratory experiments, however, have been partially successful when inert liquid or gaseous diluents have been used. Fluorinated refrigerants and liquefied HF are recommended[27] for liquid phase fluorination, while nitrogen is satisfactory in the vapor phase with reaction occurring at the surface of a copper gauze.[28] Simons and Block[29] have synthesized fluorocarbon mixtures by a continuous reaction between fluorine and carbon in a copper tube at elevated temperature with mercury salts present.

Hydrogen fluoride adds to acetylenes and olefins according to Markovnikov's rule. Catalysts are not needed, the reaction is reversible, and polymerization frequently occurs. Grosse and Lind[30] describe the preparation of ethyl fluoride in 81% yield from ethylene under pressure at 90°C. Under similar conditions propylene and hydrogen fluoride give isopropylfluoride in 61% yield.

Great advances have been made in the preparation of organic fluorides by reaction of organic halides or polyhalides with inorganic fluorides. Of especial importance as reagents in these conversions are mercury, silver, antimony, and hydrogen fluorides. World War II gave tremendous impetus to these studies, but unfortunately the vast majority of the work is only now appearing in the literature. Excellent reviews of the older and newer methods of fluorine chemistry will be found in the chapter in this book by Bockemüller and the chapter elsewhere by Henne.[31] Finger[32] has reviewed the general uses of fluorine compounds, while Wiechert and Kurt[33] have summarized the uses of HF as a condensation catalyst in organic reactions.

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[25] *Ind. Eng. Chem.*, **33**, 176, 181 (1941).

[26] McBee and Hass, *Ind. Eng. Chem.*, **33**, 137 (1941).

[27] Calcott and Benning, U. S. Patent, 2,013,030.

[28] Dimroth and Bockemüller, *Ber.*, **64**, 516 (1931). Bigelow *et al.*, *J. Am. Chem. Soc.*, **59**, 198, 2072 (1937); **60**, 427 (1938); **61**, 3552 (1939); **62**, 267, 1171, 3302 (1940); **63**, 788, 2792 (1941).

[29] *J. Am. Chem. Soc.*, **61**, 2962 (1939).

[30] *J. Org. Chem.*, **3**, 26 (1938).

[31] Henne, "The Preparation of Aliphatic Fluorine Compounds," in *Organic Reactions*, Wiley, New York, 1944, Vol. II, Chapter 2.

[32] *Chem. & Met. Eng.*, **51**, 101 (1944).

[33] *Die Chemie*, **56**, 333–342 (1943).

III. NITRATION

The nitration of aliphatic hydrocarbons with nitric acid is essentially more difficult to accomplish than it is in the aromatic series. The lower paraffin hydrocarbons are not attacked at ordinary temperatures by concentrated nitric acid or by nitric-sulfuric acid mixtures. Hydrocarbons of more than 5 carbon atoms can be converted into nitro compounds in fair yields by nitrating at elevated temperatures. The reaction is usually accompanied by oxidation. Thus Konovalov[34] obtained 2-nitrohexane in 60% yield by heating *n*-hexane in sealed tubes at 140°C. with nitric acid of a specific gravity of 1.075. Worstall[35] nitrated hydrocarbons from hexane to dodecane with nitric acid of various strengths and obtained mixtures of mono- and dinitro compounds.

Recently Hass and co-workers[36] have developed a vapor phase nitration method for preparing aliphatic nitro compounds and have applied it extensively to the lower members of the aliphatic series. Their procedure may be illustrated as follows: The hydrocarbon to be nitrated is bubbled in vapor form through concentrated nitric acid at 108°C. The gaseous mixture, which should contain the hydrocarbon and the nitric acid in approximately a 2:1 molar ratio, is led through a reaction coil heated in a molten salt bath to 420°C. The gases escaping are condensed and the organic layer containing the nitroparaffins separated from the aqueous layer containing nitric acid and small amounts of water-soluble by-products such as carboxylic acids and ketones. The yield of nitrohydrocarbons (per pass) is 20 to 30% of theory.

The nitration products are mixtures containing all of the possible mononitro substitution products which could result by replacing any hydrogen or any alkyl group in the original hydrocarbon by the nitro group. Thus, for example, *n*-butane yields 27% 1-nitrobutane, 50% 2-nitrobutane, 5% 1-nitropropane, 12% nitroethane, and 6% nitromethane.[37] No dinitroparaffins are formed at temperatures above 248°C. Even when nitroparaffins are used as reactants, they are pyrolyzed and oxidized but not nitrated.

Vapor phase nitration of methane homologues probably proceeds by free radical mechanisms although no published theory adequately accounts for all of the known facts.[38] In a private communication Hass has stated that he favors the following interpretations. (*a*) Substitution of hydrogen atoms by nitro groups:

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[34] *J. Russ. Phys. Chem. Soc.*, 25, 472 (1893); *Ber.*, 28, 878 (1893).

[35] *Am. Chem. J.*, 21, 210, 218 (1899).

[36] Hass and Riley, *Chem. Revs.*, 32, 373-430 (1943).

[37] McCleary and Degering, *Ind. Eng. Chem.*, 30, 64 (1938).

[38] Private communication.

$$RH + OH \longrightarrow R + H_2O$$

$$R + HNO_3 \longrightarrow RNO_2 + OH$$

$$NO + OH \longrightarrow HNO_2 \longrightarrow H_2O + NO + NO_2$$

These equations are consonant with the facts that primary, secondary, tertiary, neo, and bridgehead hydrogens are substituted at similar rates, and that such substitutions do not involve carbon-skeleton rearrangements of neo structures. (*b*) Substitution of alkyl groups by nitro groups.

$$R{-}R \longrightarrow 2R$$

$$R + HNO_3 \longrightarrow RNO_2 + OH$$

$$OH + NO \longrightarrow HNO_2 \longrightarrow H_2O + NO + NO_2$$

The nonformation of optically active 2-nitrobutane from active 3-methylhexane, the absence of lower nitro derivatives from cycloalkanes, and the fact that dinitro alkanes are never obtained in vapor phase nitrations are believed to be compatible with the proposed equations.

Nitration may be accomplished in the vapor phase at temperatures ranging from 248° to over 600°C., although the range 400° to 450° is favored. Higher temperatures increase the velocity of the reaction and favor the production of primary nitroparaffins and fission products, but they also lead to an undesirable pyrolysis of the nitroparaffins. For this reason temperatures are carefully controlled in the industrial process. Higher pressures increase markedly the rate of reaction, usually without greatly affecting the conversion. Under favorable conditions 40% of the nitric acid is converted to nitroparaffins, but with recovery and reoxidation of the nitric oxide produced as a by-product 90 moles of nitroparaffin can be produced for each 100 moles of nitric acid consumed.

As might be expected, methane requires more drastic conditions for its nitration than do other hydrocarbons.[39] Nitromethane is, however, produced in 15% yield in the nitration of propane.

The new method of vapor phase nitration has made readily available for the first time a whole series of new products. Industrial uses of the nitroparaffins themselves have been discussed by Gabriel.[40] Although valuable as solvents, the most important uses of the nitroparaffins at present are as chemical intermediates. Thus they may be reduced to amines, alkylhydroxylamines, or oximes. With mineral acids, they are converted in yields of 90% or more to carboxylic acids and hydroxylamine salts:

$$RCH_2NO_2 + H_2O + H_2SO_4 \longrightarrow RCO_2H + NH_3OH{\cdot}HSO_4$$

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[39] Landon, U. S. Patents, 2,161,475 and 2,164,774.

[40] *Chem. Industries*, **45**, 664 (1939); *Ind. Eng. Chem.*, **32**, 887 (1940).

For some time this reaction has served as the commercial source of hydroxylamine salts in the United States. Hydroxamic acids are formed as intermediates in the process and may be isolated under suitable conditions in 50% yields.

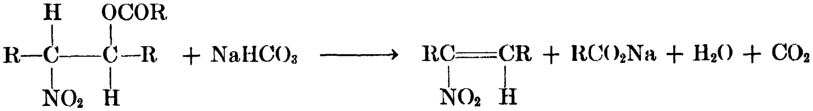
The direct halogenation of nitroparaffins may be accomplished especially easily in basic solution. The products have insecticidal properties, act as selective solvents,[41] and are powerful antigelling agents in ultra-accelerated rubber cements.

Condensation of nitroparaffins with aldehydes produces nitro alcohols:

$$RCH_2NO_2 + CH_2O \longrightarrow RCHNO_2CH_2OH$$

$$RCH_2NO_2 + 2CH_2O \longrightarrow RCNO_2(CH_2OH)_2$$

which may be esterified with either organic or inorganic acids. The nitrates of some are desirable explosives. The phosphate esters have been studied as plasticizers.[42] The reaction of the organic esters with bases provides a general means of preparing nitroolefins. Nitro alcohols are reduced to amino alcohols industrially and the products are used in making emulsifying agents and pharmaceuticals.



$$R-\underset{NO_2}{\overset{H}{C}}-\underset{H}{\overset{OCOR}{C}}-R + NaHCO_3 \longrightarrow R\underset{NO_2}{C}=\underset{H}{C}R + RCO_2Na + H_2O + CO_2$$

Nitroparaffins contain active hydrogen atoms and hence are able to add to various unsaturated compounds such as nitroolefins, α,β-unsaturated ketones, esters, and nitriles.[43]

IV. SULFONATION

The direct introduction of sulfonic acid groups, which is so simple in the aromatic series, cannot be accomplished in the aliphatic series except in certain instances. The action of sulfuric acid, chlorosulfonic acid, and related sulfonating agents on paraffins, olefins, esters, etc., usually leads to true sulfonic acids in only insignificant yields. The products are, moreover, difficult to separate from the alcohol sulfates which are formed simultaneously. More favorable results are obtained by the reaction of alkyl halides or olefins with bisulfites. However, these well known methods are not always applicable and depend for their success upon intermediates of suitable structure. It is therefore important that a simple and generally applicable method has been developed recently for the introduction of sulfonic acid groups into aliphatic compounds. Johnson and Sprague[44] found that chlorine in aqueous solution in the cold will convert alkylisothioureas into sulfonic acid chlorides.

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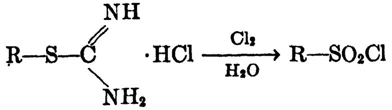
[41] Hixon and Miller, U. S. Patent, 2,138,166.
[42] Vanderbilt, U. S. Patent, 2,177,757.
[43] Kohler, *J. Am. Chem. Soc.*, 38, 889 (1916).

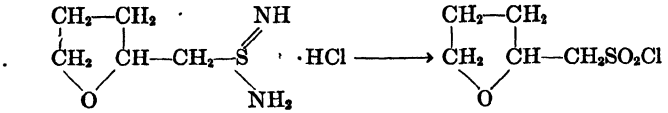


$$R{-}S{-}C\begin{matrix}{=}NH\\ {-}NH_2\end{matrix}\cdot HCl \xrightarrow[H_2O]{Cl_2} R{-}SO_2Cl$$

Similarly bromine gives the corresponding acid bromide. The general reaction was developed from an early observation of Rathke,[45] who prepared ethanesulfonic acid by the action of chlorine on *S*-ethyldiphenylthiourea in aqueous solution. Johnson and Sprague have prepared a large number of aliphatic and cycloaliphatic sulfonic acid chlorides, usually in very good yields. Thus methanesulfonic acid chloride was obtained in 76% yield from methylisothiourea. The yields are good for primary alkyl groups, poor for secondary, and zero for tertiary groups.

The starting materials for this synthesis may be obtained through the reaction of alkyl halides with thiourea or by Stevens' method[46] from alcohols and thiourea salts. If the latter method is used, it is not necessary to isolate the alkylated thiourea, and the sulfonic acid chloride may be obtained in one step from the corresponding alcohol.

In a later publication the authors describe the application of the procedure to higher molecular weight substances, such as dodecylisothiourea.[47] The synthesis has been applied to chlorinated paraffins and petroleum fractions.[48] Substituted thioureas with hetero atoms in the side chain can also be converted into sulfonic acid chlorides.[49]



The method has been extended to other sulfur compounds such as mercaptans, sulfides, alkyl thiosulfates, and related compounds.[50] All of these are converted to the corresponding sulfonic acid chlorides by the action of chlorine in aqueous solution. If alkyl thiocyanates are used, the reaction proceeds with the formation of chlorocyanogen.

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[44] *J. Am. Chem. Soc.*, 58, 1348 (1936); 59, 1837, 2439 (1937); U. S. Patents 2,146,744 and 2,147,346.

[45] *Ber.*, 14, 1774 (1881).

[46] *J. Chem. Soc.*, 81, 79 (1902).

[47] *J. Am. Chem. Soc.*, 59, 1837 (1937).

[48] U. S. Patent, 2,142,934.

[49] *J. Am. Chem. Soc.*, 59, 2439 (1937).

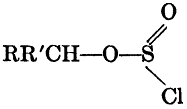
[50] *J. Am. Chem. Soc.*, 60, 1486 (1938).

$$\text{R—SCN} + \text{Cl}_2 \xrightarrow{\text{H}_2\text{O}} \text{R—SO}_2\text{Cl} + \text{ClCN}$$

The second new method for introducing sulfonic acid groups into aliphatic compounds is very remarkable. Aliphatic hydrocarbons, in liquid phase, and at ordinary or slightly elevated temperatures, react with a mixture of sulfur dioxide and chlorine in the presence of light to give sulfonic acid chlorides and hydrogen chloride.

$$\text{R—CH}_2\text{—R}' + \text{SO}_2 + \text{Cl}_2 \longrightarrow \text{RR}'\text{CH—SO}_2\text{Cl} + \text{HCl}$$

This method was discovered by Reed and first described by him in patents.[51] The reaction is applicable to aliphatic hydrocarbons from ethane and propane through octane and octadecane. The reaction mechanism is still not clear. Reed assumed that a chlorosulfinic ester (III) was formed as an intermediate but this is questionable. In many cases the reaction is complicated by a parallel reaction in which the hydrocarbon is



$$\text{RR}'\text{CH—O—S}(=\text{O})\text{—Cl}$$

(III)

chlorinated. This chlorination reaction may be suppressed by suitable reaction conditions. The reaction is of considerable importance because of its simplicity.

Kharasch and co-workers[52] have described a closely related method employing sulfuryl chloride in the presence of a base of the pyridine or quinoline type. Among many catalysts tried these were the most effective in suppressing chlorination and promoting sulfonation:

$$\text{RR}'\text{CH}_2 + \text{SO}_2\text{Cl}_2 \xrightarrow{\text{Pyridine}} \text{RR}'\text{CHSO}_2\text{Cl} + \text{HCl}$$

The reaction probably proceeds by a free radical mechanism which accounts for the relative ease of attack of aliphatic compounds and of aliphatic side chains attached to aromatic nuclei. The most favorable conditions include strong illumination and a low concentration of sulfuryl chloride. A 31% yield of sulfonation product was obtained from *n*-heptane with quinoline as catalyst and a reaction temperature of 60° to 70°C.

The authors have shown that the reaction is not limited to hydrocarbons but may be applied to acids and acid chlorides.[53] Acetic acid and acetyl chloride are chlorinated only, but the higher acids react vigorously to form cyclic β- or γ-sulfo anhydrides (Eq. 1). The α-isomer is not formed in any case, but acids such as lauric probably substitute at a number of different positions. Propionic acid reacts at 50° to 60°C. in the light

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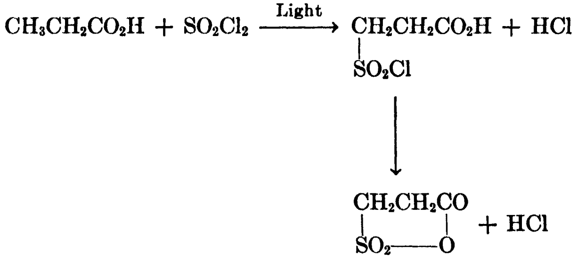
[51] U. S. Patents, 2,046,090, 2,174,492, 2,228,598 and 2,239,974.

[52] *J. Am. Chem. Soc.*, **61**, 3089 (1939).

[53] Kharasch and Brown, *J. Am. Chem. Soc.*, **62**, 925 (1940). Kharasch, Chao, and Brown, *ibid.*, **62**, 2393 (1940).



$$CH_3CH_2CO_2H + SO_2Cl_2 \xrightarrow{\text{Light}} \underset{\displaystyle SO_2Cl}{CH_2}CH_2CO_2H + HCl \longrightarrow \begin{array}{l} CH_2CH_2CO \\ SO_2\text{——}O \end{array} + HCl \qquad (1)$$

of a 200 to 300 watt incandescent bulb to form β-sulfopropionic anhydride in 52% yield. The reaction is complete in 3 or 4 hours.

Baumgarten[54] in a review of sulfonation discusses the use of sulfur trioxide addition products with hydrogen chloride, hydrogen fluoride, chlorides, fluorides, fluoborates, dioxane, and tertiary amines, and points out that free sulfur trioxide can be used to a greater extent than was previously believed. Brown[55] summarizes the uses of sulfuryl chloride in the chlorination and sulfonation of aliphatic and aromatic compounds. In a very complete compendium Suter[56] has reviewed critically the chemistry of organic compounds which are, in a broad sense, derivatives of sulfuric acid.

V. ALCOHOLS

The conversion of unsaturated hydrocarbons to alcohols has been known in principle for a long time. Recently, however, olefins have become more readily available, especially through cracking processes, and for this reason intensive reinvestigation of the hydration process has occurred.

Two methods may be employed. (*1*) *Direct hydration*:

$$C_2H_4 + H_2O \longrightarrow C_2H_5OH$$

(*2*) *Indirect hydration*: conversion of the olefin to a mineral acid ester and hydrolysis of this ester:

$$C_2H_4 + H_2SO_4 \longrightarrow C_2H_5OSO_3H$$

$$C_2H_5OSO_3H + H_2O \longrightarrow H_2SO_4 + C_2H_5OH$$

A combination of these two processes in which hydration is accomplished with a dilute mineral acid is also used. A mineral acid ester may be formed as an intermediate in this variation. For both processes numerous catalysts have been proposed and studies have been made of the reaction kinetics.[57] Ethylene and propylene are the hydrocarbons of primary interest industrially. Details of the processes cannot be described here, but a good literature review of the subject has been compiled by Ellis.[58]

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[54] *Die Chemie*, **55**, 115 (1942).

[55] *Ind. Eng. Chem.*, **36**, 785 (1944).

[56] Suter, *Organic Chemistry of Sulfur*, Wiley, New York, 1944.

A valuable new approach to the reduction of aldehydes and ketones to alcohols was discovered independently by Meerwein,[59] Ponndorf,[60] and Verley,[61] who found that aluminum alkoxides catalytically equilibrate mixtures of carbonyl compounds and alcohols:

$$\text{RR'CO} + \text{R''R'''CHOH} \xrightleftharpoons[\text{alkoxides}]{\text{Aluminum}} \text{RR'CHOH} + \text{R''R'''CO}$$

By suitable choice of reagents and conditions the desired product may be isolated in excellent yields. Lund[62] studied the scope and limitations of the reaction with a variety of aldehydes and ketones. The reduction is so specific that it may be accomplished satisfactorily in the presence of α,β unsaturation, nitro groups, ester groups, acetal groups, and reactive halogens. Pinacol formation does not interfere.

Aluminum isopropoxide possesses certain advantages over other alkoxides, and isopropyl alcohol is the usual solvent. In general the yields in aluminum isopropoxide reductions average 80 to 100% for simple aldehydes and ketones. Crotonaldehyde heated with aluminum isopropoxide in isopropyl alcohol under such conditions that the acetone formed is distilled from the mixture forms crotyl alcohol in 60% yield in 8 or 9 hours.

An alcohol may be oxidized to the corresponding aldehyde or ketone by converting it to its aluminum derivative and heating with a large excess of acetone or cyclohexanone. Adkins[63] has determined the relative oxidation-reduction potentials of a number of carbonyl-alcohol systems by equilibrations in the presence of aluminum alcoholates. Excellent reviews of this method of reduction are available.[64,65]

The third new method for the preparation of alcohols is by the catalytic reduction of carboxylic acids and their esters. This method of preparing alcohols has become more and more important in recent years, especially in chemical industry. It has, in many cases, replaced the classical reduction of esters with sodium discovered by Bouveault and Blanc.[66] It was shown by Christiansen,[67] Schmidt,[68] Schrauth, Schenck, and Stickdorn,[69] as well as by Normann[70] that esters, especially those of high molecular weight acids, may be hydrogenated to the corresponding alcohols at elevated temperatures under normal or increased pressures in the presence of suitable catalysts.

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[57] Marek and Flege, *Ind. Eng. Chem.*, **24**, 1428 (1932); Stanley *et al.*, *J. Soc. Chem. Ind.*, **53**, 205T (1934).

[58] *The Chemistry of Petroleum Derivatives*, 2nd ed., Reinhold, New York, 1937.

[59] Meerwein and Schmidt, *Ann.*, **444**, 221 (1925).

[60] *Z. angew. Chem.*, **39**, 138 (1926).

[61] *Bull. soc. chim.*, **37**, 537, 871 (1925); **41**, 788 (1927).

[62] *Ber.*, **70**, 1520 (1937).

[63] *J. Am. Chem. Soc.*, **60**, 1151 (1938); **61**, 3364 (1939); **62**, 3305 (1940).

[64] Wilds, "Reduction with Aluminum Alkoxides (The Meerwein-Ponndorf-Verley Reduction)," in *Organic Reactions*, Wiley, New York, 1944, Vol. II, Chapter 5.

[65] *Angew. Chem.*, **58**, 266 (1940).

[66] *Compt. rend.*, **136**, 1676 (1903); **137**, 60 (1903).

Fatty alcohols, which have attained great importance as raw materials in the manufacture of detergents, are now technically available by this process. A further development of the method has been made by Adkins and Folkers,[71] who in 1932 described its application to the esters of the lower mono- and dicarboxylic acids. They have studied intensively the influence of temperature, pressure, catalysts, solvents, and other variables. The reduction proceeds under very energetic conditions, and especially with high molecular weight esters, to the corresponding hydrocarbons. Through the use of highly active catalysts, it has been found possible to lower considerably the temperatures and pressures originally employed and to increase the yield of alcohols. Numerous patents emphasize the great technical importance of this reaction.[72] Catalysts include cadmium, chromium, copper, zinc, iron, nickel, cobalt, and lead salts of the acids. The reduction is accomplished at temperatures of 240° to 400°C. and under pressures of 2000 pounds. Unsaturated alcohols, such as oleyl alcohols, may be satisfactorily prepared. The discovery of paraffin oxidation methods for preparing fatty acids has increased still further industrial interest in this process.

A synthetic method (Eq. 2) developed in Germany consists in the addition of carbon monoxide and hydrogen to olefins with subsequent hydrogenation to yield aldehydes and alcohols.[73] Information on this process was recently summarized.[73a]

$$\begin{aligned} RCH{=}CH_2 + CO + H_2 &\longrightarrow RCH(CH_3)CHO \\ RCH(CH_3)CHO + H_2 &\longrightarrow RCH(CH_3)CH_2OH \end{aligned} \tag{2}$$

The oxidation of paraffins with atmospheric oxygen yields mixtures of alcohols as well as other products. Nametkin and Teneva[74] have isolated all of the normal alcohols from propyl through stearyl from paraffin oxidized in this manner commercially on a large scale in Russia.

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[67] U. S. Patent, 1,302,011.

[68] *Ber.*, 64, 2051 (1931).

[69] *Ber.*, 64, 1314 (1931).

[70] *Angew. Chem.*, 44 714 (1931).

[71] *J. Am. Chem. Soc.*, 53, 1095 (1931); 54, 1145 (1932).

[72] U. S. Patents, 2,322,095-2,322,099, 2,340,343, 2,340,344 and 2,340,687-2,340,691

[73] *Chem. Abstracts*, 38 4252 (1944).

[73a] Office of the Publication Board, Dept. of Commerce, Washington, D. C., PB-27713.

[74] *J. Gen. Chem. U. S. S. R.*, 12, 229 (1942); *Chem. Abstracts*, 37, 3254 (1943).

VI. ETHERS

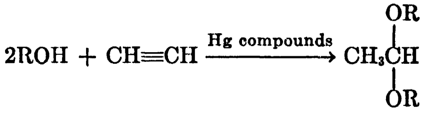
In the field of aliphatic ether synthesis there are two new reactions to be discussed.

1. Addition of α-Halogenated Ethers to Olefins. According to Scott[75] α-halogenated ethers, such as monochloromethyl ether, add readily to olefins:

$$CH_3—O—CH_2Cl + CH_2{=}CH_2 \longrightarrow CH_3—O—CH_2CH_2CH_2Cl$$

In many cases the use of catalysts, especially metal halides, is advantageous.[76] The reaction was discovered independently by F. Straus[77] and extended to dienes. The new ethers may be subjected to dehydrohalogenation and other reactions of value in organic syntheses.

2. Preparation of Vinyl Ethers from Alcohols and Acetylene. The Reppe Process.[78] It has been known for some time that acetylene adds to alcohols in the presence of catalysts, especially mercury compounds, to form acetals:



$$2ROH + CH{\equiv}CH \xrightarrow{\text{Hg compounds}} CH_3CH\begin{matrix}OR\\ |\\ \\ |\\ OR\end{matrix}$$

At elevated temperatures, however, and in the presence of basic compounds, such as the alkali hydroxides and cyanides, vinyl ethers are formed. The reaction often proceeds better under pressure. When this is done, the acetylene is diluted with an indifferent gas such as nitrogen to avoid the danger of an explosion. Quantitative yields have been obtained[79] and rate and mechanism studies have been made.[80]

$$ROH + CH{\equiv}CH \xrightarrow{KOH} R—O—CH{=}CH_2 \quad .$$

The reaction proceeds satisfactorily with mono- or polyhydric alcohols, as is amply illustrated by examples in the original patent. It may also be effected in the gas phase.[81] In later patents, zinc or cadmium salts or organic acids are recommended as catalysts instead of alkaline compounds.[82] Thiovinyl ethers are formed from mercaptans.[83]

VII. AMINES

Methods for the preparation of amines are relatively abundant compared to methods for the preparation of other classes of aliphatic compounds. To the classical procedures, such as the degradation of acid amides by the methods of Hofmann and Curtius, have been added the reduction of nitro compounds, nitriles, or oximes, and the addition of amines to activated double bonds. In recent years procedures have been described which are similar in principle to the old procedures, but which are easier to use and may be applied more generally.

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[75] U. S. Patent, 2,024,749.

[76] U. S. Patent, 2,143,021.

[77] *Ann.*, **525**, 151 (1936).

[78] *Chem. Zentr.*, **1932, II**, 923; *Chem. Abstracts*, **26**, 4825 (1932).

[79] *J. Gen. Chem. U. S. S. R.*, **13**, 1 (1943).

[80] *Chem. Abstracts*, **37**, 6539 (1943).

[81] *Chem. Zentr.*, **1936, II**, 3846; *Chem. Abstracts*, **30**, 2578 (1936).

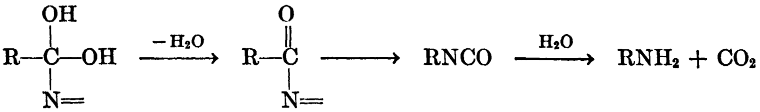
[82] British Patent, 481,389.

[83] German Patents, 617,543 and 624,845.

In the first place there is the degradation of carboxylic acids to amines by means of hydrazoic acid. This method was first described by R. F. Schmidt[84] in a patent. Carboxylic acids, dissolved in concentrated sulfuric acid, react with a 10% solution of hydrazoic acid at 40° to 45°C., evolving nitrogen and carbon dioxide and forming the amine (sulfate):

$$RCH_2CO_2H + HN_3 \longrightarrow RCH_2NH_2 + CO_2 + N_2$$

The mechanism of the reaction has not been definitely determined. Schmidt proposes two possible mechanisms: (*1*) Addition of imine (=NH), formed from the hydrazoic acid, to the C=O group of the carboxyl group, followed by elimination of water and rearrangement to an isocyanate:



$$R-\underset{\displaystyle N=}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}-OH \xrightarrow{-H_2O} R-\underset{\displaystyle N=}{\overset{\displaystyle O}{\overset{\|}{\underset{|}{C}}}} \longrightarrow RNCO \xrightarrow{H_2O} RNH_2 + CO_2$$

(*2*) As in the Curtius degradation, formation of an acid azide which decomposes to an amine and carbon dioxide via the isocyanate:

$$RCON_3 \longrightarrow RCON{=} + N_2 \longrightarrow RNCO \xrightarrow{+H_2O} RNH_2 + CO_2$$

By this method aniline is obtained in 80% yield from benzoic acid and tetramethylenediamine in 83% yield from adipic acid. Complete experimental details have been given by von Braun,[85] who extended the method to cycloaliphatic compounds. Osterlin[86] has also described a number of examples of the reaction. He finds that the method fails with many substituted carboxylic acids, especially those in the heterocyclic series. The sulfonating and cleaving action of the sulfuric acid may cause trouble with certain substituted acids. However, no other suitable solvent for the reaction is known. Osterlin avoids the handling of free hydrazoic acid by adding sodium azide to a solution of the carboxylic acid in concentrated sulfuric acid overlayered with chloroform. This modification greatly improves the ease with which the reaction is run. Osterlin's modification was used by Miller and Bachman[87] in preparing substituted aminobenzophenones. The Hofmann, Schmidt, and Curtius reactions have recently been carefully reviewed.[87a]

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[84] German Patent, 500,435.

[85] *Ann.*, **490**, 125 (1931); *Ber.*, **64**, 2866 (1931).

[86] *Angew. Chem.*, **45**, 536 (1932).

[87] *J. Am. Chem. Soc.*, **57**, 2443 (1935).

A similar synthesis, but one which resembles the Curtius degradation more closely, has been described in several publications by Naegeli and coworkers.[88] Acid chlorides react with sodium azide in indifferent solvents and at moderately elevated temperatures to form the corresponding isocyanate. This is then hydrolyzed by dilute acids to the amine.

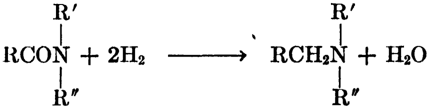
$$RCH_2COCl + NaN_3 \longrightarrow RCH_2CON_3 + NaCl$$

$$RCH_2CON_3 \longrightarrow RCH_2NCO + N_2$$

$$RCH_2NCO + H_2O \longrightarrow RCH_2NH_2 + CO_2$$

The method gives good yields of amines from aliphatic mono- and dicarboxylic acids,[89] and is also useful in obtaining isocyanates.[90,91] Sometimes technical sodium azide reacts more sluggishly than freshly prepared material. Nelles[92] has found that in such cases the technical sodium azide may be activated with hydrazine hydrate.

Although the catalytic hydrogenation of oximes and nitriles has been known for some time, it has only recently been shown by Adkins and Wojcik[93] that amides can also be hydrogenated to amines catalytically. The process does not proceed as uniformly as do other hydrogenations. In addition to the desired reaction (Eq. 3), there are also side reactions, such



$$RCO\overset{\displaystyle R'}{\underset{\displaystyle R''}{N}} + 2H_2 \longrightarrow RCH_2\overset{\displaystyle R'}{\underset{\displaystyle R''}{N}} + H_2O \qquad (3)$$

as the cleavage of the amine group, dealkylation, formation of secondary amines, etc. These depress the yields, and with certain amides, especially the alkylated amides, may lead to only minor amounts of the desired product. However, lauric and heptanoic acid amides give yields of 40 to 70% of the corresponding amine. The reduction proceeds especially well in dioxane at 175° to 250°C. under 100 to 300 atmospheres pressure with a copper chromite catalyst.

Catalytic hydrogenation of nitriles yields not only primary amines but also the corresponding secondary amines (Eq. 4). Basic conditions are

$$RCN + H_2(\text{catalyst}) \longrightarrow RCH_2NH_2 + (RCH_2)_2NH \qquad (4)$$

[87a] *Organic Reactions*, Wiley, New York, 1946, Vol. III, Chapters 7, 8, and 9.
[88] *Helv. Chim. Acta*, **12**, 227 (1929).
[89] Naegeli and Lendorff, *Helv. Chim. Acta*, **15**, 49 (1932).
[90] Schroeter, *Ber.*, **42**, 3356 (1909).
[91] Boehmer, *Rec. trav. chim.*, **55**, 379 (1936).
[92] *Ber.*, **65**, 1345 (1932).
[93] *J. Am. Chem. Soc.*, **56**, 247 (1934).

favored to avoid hydrolysis of the intermediate imines.[94] It has been shown by Mignonac[95] and by others[96] that the formation of secondary amines may be suppressed by performing the reduction in the presence of ammonia. Even dinitriles may be successfully reduced to diamines under these conditions.[97] The process may be performed in the vapor phase.[98] On the other hand, a patented process for preparing secondary amines from nitriles involves the removal of ammonia during the hydrogenation.[99] The increased availability of nitroparaffins and their reaction products has provided a good source for a variety of amines, amino alcohols, and related products.

The reaction of alkyl halides with ammonia is one of the most important methods for preparing primary amines. It is usually carried out in a solvent such as water or alcohol, and under such conditions often leads to secondary amines more readily than to primary amines. It was shown by von Braun[100] that this difficulty may be avoided, especially with the higher halides, by the use of liquid ammonia under pressure. Similarly Bersworth[101] recommends the use of anhydrous ammonia and a temperature of 150°C. for the preparation of ethylenediamine from ethylene chloride. In this method, as in other similar methods, the relative lability of the halogens is I > Br > Cl. Numerous patents indicate the importance of the method.[102]

The results of Lebeau[103] and Chablay[104] on the reaction of sodium amide with alkyl halides indicate that saturated and unsaturated hydrocarbons are formed principally and only small amounts of amines. Shreve and Rothenberger,[105] on the other hand, using a different method of preparing their sodium amide, have found that hexylamine may be obtained in 75% yield from hexyl bromide. The preparation of sodium amide followed the procedure of Vaughn, Vogt, and Nieuwland[106] in which sodium is treated with liquid ammonia in the presence of iron nitrate as catalyst. The influence of the temperature, the solvent, and the type of halide was studied. It would be interesting to apply this method to instances in which other methods fail.

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[94] British Patent, 536,940.

[95] British Patent, 282,083.

[96] Schwoegler and Adkins, *J. Am. Chem. Soc.*, **61**, 3499 (1939). Robinson and Snyder, *Org. Syntheses*, **23**, 71 (1943). Bachman and Mayhew, *J. Org. Chem.*, **10**, 245 (1945).

[97] Canadian Patents, 408,981 and 408,983.

[98] French Patent, 851,748.

[99] U. S. Patent, 2,355,356.

[100] *Ber.*, **70**, 979 (1937).

[101] U. S. Patent, 2,028,041.

[102] U. S. Patent, 2,305,830.

[103] *Compt. rend.*, **140**, 1042, 1264 (1905).

[104] *Compt. rend.*, **156**, 327 (1913); *Ann. chim.*, **1**, 469 (1914).

[105] *Ind. Eng. Chem.*, **29**, 1361 (1937).

[106] *J. Am. Chem. Soc.*, **56**, 2120 (1934).

The replacement of hydroxyl groups by amino or alkylamino groups has attracted great technical interest since the discovery by Sabatier of a suitable catalyst for the reaction. The lower alcohols are converted to amines by reaction with ammonia or primary or secondary amines in the vapor phase over dehydrating catalysts such as ThO_2, Al_2O_3, W_2O_5, etc.[107] In recent times this method has been refined through the use of improved catalysts[108] and conditions.[109] Even the preparation of the higher primary, secondary, and tertiary amines has succeeded. Thus the higher fatty alcohols yield fatty amines in a sealed tube at 300° to 400°C. under 50 atmospheres pressure with aluminum oxide as catalyst.[110] Similar products have also been prepared by carrying out the reaction in the vapor phase.[111]

In summary, it may be said that the catalytic conversion of alcohols to amines generally proceeds with good yields. However, the most favorable catalyst to use depends on the reaction conditions, the nature of the starting materials, and the desired end-products. Reductive alkylation of ammonia, amines, or nitriles may be accomplished in the presence of aldehydes or ketones, hydrogenation catalysts, and hydrogen. By suitably varying the proportion of carbonyl compound to *N*-derivative either primary, secondary, or tertiary amines may be obtained.[112]

The use of the Grignard reagent in preparing amines has been applied in several different ways. It has been found[113] that *O*-alkylhydroxylamines give good yields of primary amines according to Equation (5). The yields

$$RONH_2 + R'MgX \longrightarrow R'NH_2 + ROMgX \qquad (5)$$

depend on the nature of X, decreasing strongly from chlorine to iodine. Where R is the methyl or benzyl radical, yields average 65 to 75%. R'MgX may be satisfactorily replaced by R'Li.

Secondary and tertiary amines (Eqs. 6) are obtained from primary or secondary amines by a process devised by Prévost and Cerf de Mauny.[114]

$$\begin{aligned} RR'NH + CH_2O &\longrightarrow RR'NCH_2OH \\ RR'NCH_2OH + HCl &\longrightarrow RR'NCH_2Cl\cdot HCl + H_2O \qquad (6) \\ RR'NCH_2Cl + R''MgX &\longrightarrow RR'NCH_2R'' + MgXCl \end{aligned}$$

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[107] Sabatier and Reid, *Catalysis in Organic Chemistry*, Van Nostrand, New York, 1923.

[108] Groggins and Stirton, *Ind. Eng. Chem.*, **29**, 1353 (1937).

[109] U. S. Patent, 2,312,754.

[110] French Patent, 779,913.

[111] U. S. Patent, 2,078,922.

[112] Henze and Humphreys, *J. Am. Chem. Soc.*, **64**, 2878 (1942); U. S. Patent, 2,298,284; Canadian Patent, 409,004. Campbell, Sommers, and Campbell, *J. Am. Chem. Soc.*, **66**, 82 (1944); U. S. Patents, 2,278,372 and 2,278,373; British Patent, 542,609.

[113] Sheverdina and Kocheskhov, *J. Gen. Chem.*, *U. S. S. R.*, **8**, 1825 (1938) [*Chem. Abstracts*, **33**, 5804 (1939)]; *Bull. acad. sci. U. R. S. S., Classe sci. chim.*, **1941**, 75 [*Chem. Abstracts*, **37**, 3066 (1943)].

[114] *Compt. rend.*, **216**, 771 (1943).

Neither the hydroxymethyl- nor chloromethylamines are isolated. The first step is carried out in aqueous mixture; the product is salted-out with potassium carbonate and dissolved in benzene. The second step is accomplished by saturating the benzene solution with gaseous hydrogen chloride. The chloride hydrochloride so formed is treated with a large excess of the Grignard reagent to complete the final step. The method has not been adequately evaluated but appears to give good yields.

Marxer[115] has prepared a series of amino alcohols by reaction of $R_2N(CH_2)_nMgX$ with ketones. The formation of the Grignard reagent is dependent on n being large enough (*i.e.*, at least 3).

The Mannich condensation of amines with active hydrogen compounds in the presence of formaldehyde has made available a broad series of compounds containing amine groups. The reaction may be exemplified by Equation (7). An excellent review of this method has been prepared by Blicke.[116] The reaction is also applicable to nitroparaffins.[117]

$$CH_3COCH_3 + CH_2O + R_2NH \longrightarrow CH_3COCH_2CH_2NR_2 + H_2O \qquad (7)$$

A review of industrial processes for the production of amines by ammonolysis has been prepared by Mayor.[118]

VIII. ALDEHYDES AND KETONES

The conversion of alcohols to aldehydes and ketones through dehydrogenation has been developed industrially especially in countries which are amply supplied with petroleum and the olefins derived from it. Olefins are readily hydrated to the alcohols needed as raw materials. The conversion of propylene to isopropyl alcohol and thence to acetone is a process which competes in cost with the preparation of acetone by other methods.

$$CH_3CH{=}CH_2 + H_2O \xrightarrow{H^+} CH_3CHOHCH_3$$

$$CH_3CHOHCH_3 \xrightarrow{\text{Catalyst}} CH_3COCH_3 + H_2$$

The conversion of secondary alcohols to ketones can be accomplished by dehydrogenation, oxidation, or a combination of these two processes. Since the dehydrogenation is endothermic, while the oxidation is exothermic, it is possible to work out a favorable thermal balance by utilizing both reactions simultaneously. In recent years a large number of new catalysts have been recommended.

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[115] *Helv. Chim. Acta*, 24, 209E (1941).

[116] Blicke, "The Mannich Reaction," in *Organic Reactions*, Wiley, New York, 1942, Vol. I, Chapter 10.

[117] Bachman and Cooper, *J. Org. Chem.*, 9, 307 (1944); Bachman and Mayhew, *J. Org. Chem.*, 10, 244 (1945).

[118] *Industrie chimique*, 28, 206 (1941).

Sabatier and Senderens[119] originally proposed metallic copper. The newer catalysts include sulfides, phosphides, and selenides of zinc, cadmium, cobalt, iron, and aluminum.[120] Metal alloys, such as a copper-zinc alloy, have been recommended as long-lived catalysts which suppress side reactions, especially olefin formation.[121] According to Taylor and Lazier,[122] zinc oxide or zinc oxide containing 4.5% sodium hydroxide is an excellent catalyst. With its aid 95 to 99% yields of acetone are obtained from isopropyl alcohol at 400°C. in the vapor phase. Higher ketones, valuable as solvents in the lacquer industry, can also be prepared by dehydrogenation methods. Thus 2-pentanone has been obtained from 2-pentanol[123] and 4-heptanone from 1-butanol.[124] Badin has recently studied the liquid phase dehydrogenation of a series of aliphatic primary alcohols with Raney nickel as catalyst.[125] Paraffins and olefins are also formed. Cozzi has similarly studied the use of vanadium pentoxide for dehydrogenation of alcohols.[126]

A whole series of patents has appeared describing the oxidative conversion of alcohols to ketones with air or oxygen. Sabatier and Senderens used copper, nickel, cobalt, or platinum as catalyst.[127] Simington and Adkins[128] have reported a large number of comparative experiments on this method. Cardarelli[129] recommends passing isopropyl alcohol and the calculated amount of oxygen over copper at 225 to 350°C. The temperature is regulated with the aid of a liquid of suitable boiling point, such as biphenyl. Other recently recommended catalysts include the trioxides of molybdenum and tungsten[130] and a copper-silver catalyst supported on pumice.[131]

A method which is still important for the preparation of aliphatic ketones is the one starting with carboxylic acids. This method is becoming even more prominent because of the newly available preparations of carboxylic acids, *i.e.*, by paraffin oxidation, or by the reaction of olefins with carbon monoxide and water under pressure. In many cases the old method of calcium salt distillation has been displaced by the catalytic method. For use in the gas phase the following catalysts have been proposed: oxides, such as those of thorium and uranium,[132] manganese compounds,[133] and calcium and barium compounds supported on aluminum. For higher ketones Tressler[134] recommends iron oxide at 200° to 320°C. in the presence of carbon dioxide. The carboxylic acids, under diminished or increased pressure, are led over the catalyst as such or supported on silica gel, clay, carbon, etc.

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[119] *Ann. chim. phys.*, **4**, 459 (1905).
[120] British Patents, 262,120 and 263,877.
[121] U. S. Patent, 1,952,702.
[122] U. S. Patents, 1,895,516, 1,895,528 and 1,895,529.
[123] U. S. Patent, 2,028,267.
[124] Canadian Patent, 321,645.
[125] *J. Am. Chem. Soc.*, **65**, 1809 (1943).
[126] *Chem. Abstracts*, **38**, 4499 (1944).
[127] *Compt. rend.*, **136**, 983 (1903).
[128] *J. Am. Chem. Soc.*, **50**, 1449 (1928).
[129] U. S. Patent, 1,988,481.
[130] British Patent, 547,743.
[131] Davies and Hodgson, *J. Chem. Soc.*, **1943**, 282.

Single carboxylic acids yield symmetrical ketones with one less than twice the original number of carbon atoms. From mixtures of acids unsymmetrical ketones may be prepared, but the reaction is no longer a uniform one:

$$RCO_2H + R'CO_2H \longrightarrow R{-}CO{-}R + R{-}CO{-}R' + R'{-}CO{-}R' + CO_2 + H_2O$$

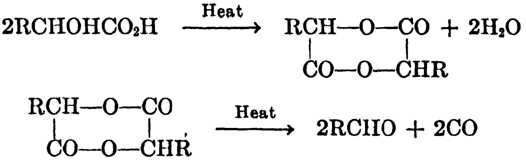
If formic acid or one of its salts is used, there is formed an aldehyde with the same number of carbon atoms as is present in the second acid:

$$RCO_2H + HCO_2H \longrightarrow RCHO + H_2O + CO_2$$

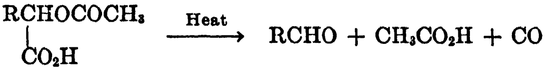
A highly recommended catalyst is titanium dioxide.[135]

In recent years the conversion of acids to aldehydes has been greatly improved by the discovery and development of new methods. These new methods are especially valuable, since they may be used to prepare sensitive end-products otherwise difficultly available. Some of the best of these new methods are described below.

α-Hydroxy acids decompose on distillation to aldehydes containing one less carbon atom. Lactides are formed as intermediates:



Thus, when R was $C_{10}H_{21}$, a yield of 96% was obtained by Davies and Hodgson.[136] This original method of Blaise[137] was extended by Bagard[138] to α-acetoxy acids and the intermediate lactide step thereby eliminated:



$$\begin{array}{l}RCHOCOCH_3\\ \mid\\ CO_2H\end{array} \xrightarrow{\text{Heat}} RCHO + CH_3CO_2H + CO$$

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[132] Senderens, *Bull. soc. chim.*, **5**, 905 (1909); Kistler, Swann, and Appel, *Ind. Eng. Chem.*, **26**, 388 (1934).

[133] Cowan, Jeffrey, and Vogel, *J. Chem. Soc.*, **1940**, 171.

[134] U. S. Patent, 1,941,640.

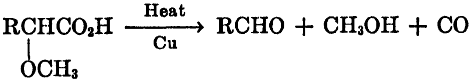
[135] Davies and Hodgson, *J. Chem. Soc.*, **1943**, 84.

[136] *J. Soc. Chem. Ind.*, **62**, 128 (1943).

[137] *Compt. rend.*, **138**, 697 (1904).

[138] *Bull. soc. chim.*, **1**, 307 (1907).

More recently Darzens[139] has applied the reaction to α-alkoxy acids. These compounds, which can be prepared from α-halogen acids and metal alcoholates, decompose to form aldehydes on distillation, especially in the presence of copper:



$$\underset{\displaystyle OCH_3}{RCHCO_2H} \xrightarrow[Cu]{Heat} RCHO + CH_3OH + CO$$

Thus hexanal was obtained in 70% yield from α-methoxyheptanoic acid.

Von Braun[140] has devised another synthesis of aldehydes from α-halogen acids (Eqs. 8). The acid chloride is allowed to react with sodium azide and after a series of intermediate steps the resulting aldehyde or ketone is isolated. If the original acid is branched at the α-position, the product is a ketone. Heptaldehyde is obtained from α-bromocaprylic acid and dibutyl ketone from α-bromodibutylacetic acid, both in 70% yield.

$$\begin{aligned} &RCHBrCOCl + NaN_3 \longrightarrow RCHBrCON_3 + NaCl \\ &RCHBrCON_3 \longrightarrow RCHBrNCO + N_2 \\ &RCHBrNCO + H_2O \longrightarrow RCHBrNH_2 + CO_2 \\ &RCHBrNH_2 + H_2O \longrightarrow RCHO + NH_4Br \end{aligned} \qquad (8)$$

Grundmann[141] has described a method for obtaining aldehydes from acid chlorides containing the same number of carbon atoms (Eqs. 9).

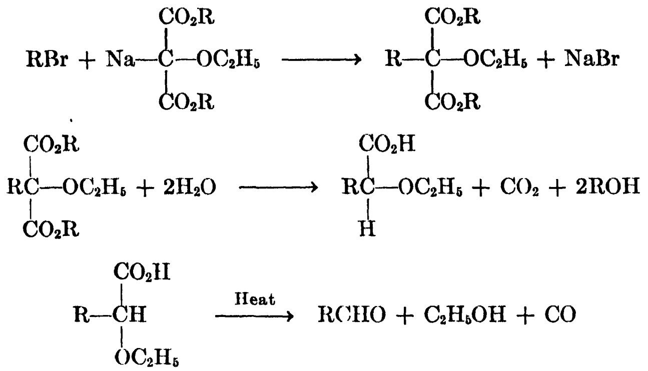
$$\begin{aligned} &RCOCl + CH_2N_2 \longrightarrow RCOCHN_2 + HCl \\ &RCOCHN_2 + CH_3CO_2H \longrightarrow RCOCH_2OCOCH_3 + N_2 \\ &RCOCH_2OCOCH_3 + H_2 \longrightarrow RCHOHCH_2OH \\ &RCHOHCH_2OH + Pb(OCOCH_3)_4 \longrightarrow RCHO + CH_2O + Pb(OCOCH_3)_2 \\ &\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad + 2CH_3CO_2H \end{aligned} \qquad (9)$$

The acid chloride is converted to a diazo ketone. This is rearranged in the presence of acetic acid to the acetate of a 1,2-hydroxy ketone which is in turn reduced with sodium amalgam or aluminum isopropylate to a 1,2-glycol. The glycol gives the desired aldehyde and formaldehyde when oxidized with lead tetraacetate by Criegee's procedure. A series of sensitive aldehydes has been prepared by this method.

Darzens' method[142] makes possible the preparation of aldehydes from alkyl halides containing one less carbon atom (Eqs. 10). It employs the decomposition of α-alkoxy acids already described. Alkyl halides react with sodium ethyl ethoxymalonate to form the corresponding alkylated

[139] *Compt. rend.*, **196**, 348 (1933).
[140] *Ber.*, **67**, 218 (1934).
[141] *Ann.*, **524**, 31 (1936).
[142] *Compt. rend.*, **196**, 489 (1933).

ester. After saponification and decarboxylation an α-alkoxy acid is obtained which decomposes on distillation to the desired aldehyde. Thus from lauryl bromide, tridecanoic aldehyde is obtained.



$$\mathrm{RBr} + \mathrm{Na}\!-\!\underset{\mathrm{CO_2R}}{\overset{\mathrm{CO_2R}}{\mathrm{C}}}\!-\!\mathrm{OC_2H_5} \longrightarrow \mathrm{R}\!-\!\underset{\mathrm{CO_2R}}{\overset{\mathrm{CO_2R}}{\mathrm{C}}}\!-\!\mathrm{OC_2H_5} + \mathrm{NaBr}$$

$$\mathrm{R}\underset{\mathrm{CO_2R}}{\overset{\mathrm{CO_2R}}{\mathrm{C}}}\!-\!\mathrm{OC_2H_5} + 2\mathrm{H_2O} \longrightarrow \mathrm{R}\underset{\mathrm{H}}{\overset{\mathrm{CO_2H}}{\mathrm{C}}}\!-\!\mathrm{OC_2H_5} + \mathrm{CO_2} + 2\mathrm{ROH} \qquad (10)$$

$$\mathrm{R}\!-\!\underset{\mathrm{OC_2H_5}}{\overset{\mathrm{CO_2H}}{\mathrm{CH}}} \xrightarrow{\text{Heat}} \mathrm{RCHO} + \mathrm{C_2H_5OH} + \mathrm{CO}$$

Some years ago Sonn and Müller[143] described the preparation of aromatic aldehydes from acid amides by way of imido chlorides. The latter are reduced to imine hydrochlorides with stannous chloride in ethereal solution and then hydrolyzed. Nelles and later von Braun found that the method could not be applied to aliphatic acid amides, since the imido chlorides of this series are unstable except those of the α,β-unsaturated acids. Unfortunately imido chlorides of α,β-unsaturated acids are not reduced by stannous chloride. More recently (Eqs. 11), however, reduction by chromous chloride has been shown by von Braun and Rudolph[144] to proceed satisfactorily and to lead to the formation of aldehydes. An arylamide of the α,β-unsaturated acid is converted by phosphorus pentachloride to the corresponding imido chloride. This is reduced in ether solution by a paste of chromous chloride, and the product is hydrolyzed with acid. Hexenal is obtained in 50% yield from 2-hexenoic acid.

$$\mathrm{RCH{=}CH{-}CO{-}NHAr} + \mathrm{PCl_5} \longrightarrow \mathrm{RCH{=}CH{-}CCl{=}NAr} + \mathrm{POCl_3}$$

$$\mathrm{RCH{=}CH{-}CCl{=}NAr} + \mathrm{CrCl_2} \longrightarrow \mathrm{RCH{=}CH{-}CH{=}NAr} + \mathrm{CrCl_3} \qquad (11)$$

$$\mathrm{RCH{=}CH{-}CH{=}NAr} + \mathrm{H_2O} \longrightarrow \mathrm{RCH{=}CH{-}CHO} + \mathrm{ArNH_2}$$

Although aliphatic imido chlorides are not reduced by stannous chloride, nitriles are smoothly converted to aldehydes by this reagent and hydrogen chloride in ether solution. This elegant method was discovered by Stephen[145] and described in 1925 (Eqs. 12). The yields are usually quite good and the reaction has been frequently employed.

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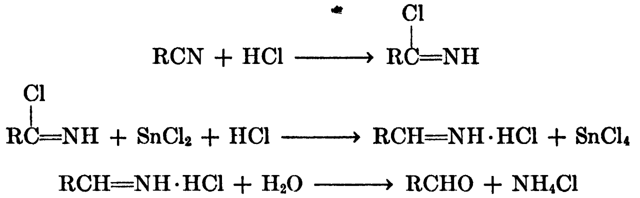
[143] *Ber.*, **52**, 1927 (1919).
[144] *Ber.*, **67**, 269, 1735 (1934).
[145] *J. Chem. Soc.*, **127**, 1875 (1925).



$$\mathrm{RCN + HCl \longrightarrow R\overset{Cl}{\overset{|}{C}}{=}NH}$$

$$\mathrm{R\overset{Cl}{\overset{|}{C}}{=}NH + SnCl_2 + HCl \longrightarrow RCH{=}NH \cdot HCl + SnCl_4} \qquad (12)$$

$$\mathrm{RCH{=}NH \cdot HCl + H_2O \longrightarrow RCHO + NH_4Cl}$$

Rosenmund has shown that the liquid phase reduction of acid chlorides to aldehydes with hydrogen in the presence of noble metal catalysts proceeds with good yields in many cases. More recently Froschl and Danoff[146] have reduced acid chlorides catalytically in the vapor phase using a palladium catalyst. They obtained good yields in the aliphatic series. Recently the reduction of acids directly with sodium amalgam has been found to give fair to good yields of aldehydes in the aliphatic series.[147]

In concluding this section a method will be described which has long been known in principle, but which has recently been improved and extended: the preparation of ketones through the addition of acid chlorides to olefins. This reaction, discovered by Kondakov[148] and later studied by Wieland and Bettag,[149] proceeds, with suitable catalysts, and yields β-chloro ketones. It represents one of the few applications of the Friedel-Crafts reaction in the aliphatic series.[150] The reaction products may undergo a number of further transformations. Thus, for example, they may be dehydrohalogenated to unsaturated ketones. This synthesis is applicable to halogenated and to unsaturated acid chlorides.[151] Nenitzescu and Cioranescu[152] have shown that halogen-free ketones may be obtained by this method if hydrogen donors are present during the reaction. Thus cyclohexyl butyl ketone is obtained from a mixture of pentanoyl chloride, cyclohexene, cyclohexane, and aluminum chloride. The condensation, which normally is run in the presence of equimolecular amounts of Friedel-Crafts type catalysts, has been shown by Frolich and Wiczevich[153] to be successful also in the presence of small amounts of catalytically active substances, such as bismuth chloride, under pressure.

$$\mathrm{CH_3COCl + CH_2{=}CH_2 \xrightarrow{AlCl_3} CH_3COCH_2CH_2Cl} \qquad (13)$$

By addition of acid chlorides to acetylenes (Eq. 14) β-chlorovinyl ketones are obtained.[154,155] Kroeger, Sowa, and Nieuwland[156] have applied the reaction to monoalkylacetylenes.

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[146] *J. prakt. Chem.*, **144**, 217 (1936).
[147] Davies and Hodgson, *J. Soc. Chem. Ind.*, **62**, 128 (1943).
[148] *Bull. soc. chim.*, **7**, 576 (1892).
[149] *Ber.*, **55**, 2246 (1922).
[150] U. S. Patent, 1,737,203; Colonge and Mostafavi, *Bull. soc. chim.*, **6**, 335, 342 (1939).
[151] British Patent, 459,537.
[152] *Ber.*, **69**, 1820 (1936).
[153] U. S. Patent, 2,006,198.

$$\mathrm{RCOCl + CH{\equiv}CH \longrightarrow RCOCH{=}CHCl} \qquad (14)$$

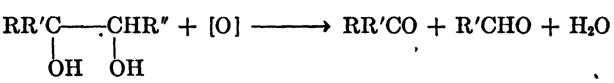
An outstanding new development in the synthesis of carbonyl compounds is the so-called Oxo process[156a] developed in Germany. In this process olefins, especially those containing $CH_2=$ groups, are combined with carbon monoxide and hydrogen (water gas) in the presence of hydrogenation catalysts of the Fischer-Tropsch type:

$$\mathrm{RCH{=}CHR + CO + H_2 \longrightarrow RCH_2CHRCHO + (RCH_2CHR)_2CO} \qquad (15)$$

Aldehydes predominate in the products. A pressure of 150 atmospheres and a temperature of 180°C. are suitable. The catalyst contains cobalt, thoria, and magnesia[157] suspended on kieselguhr and dispersed in Diesel oil. It may be re-used 50 to 100 times and is not sensitive to sulfur.[157a] Although the published information on the Oxo process is meager there is considerable industrial interest in its development.

Henne and Perilstein[158] have examined carefully the preparation of aldehydes and ketones by the long known method of ozonolysis of olefins, using a newly designed ozonizer and decomposing the ozonides by catalytic hydrogenation. They obtained good yields of aliphatic mono- and dialdehydes. Similarly, Johnson and Degering[159] have prepared a series of aliphatic aldehydes and ketones by the long known hydrolysis of nitronic acids formed from nitroparaffins. The nitroparaffin was dissolved in aqueous NaOH and this solution dropped into dilute H_2SO_4. The following yields were reported: propionaldehyde, 80%; butyraldehyde, 85%; methyl ethyl ketone, 86%; isobutyraldehyde, 32.4%. The process has also been patented.[160]

Oxidation of 1,2-dihydroxy compounds under controlled conditions yields carbonyl compounds, as for example, in Equation 16. Suitable



$$\mathrm{RR'\underset{OH}{C}{-}\underset{OH}{C}HR'' + [O] \longrightarrow RR'CO + R'CHO + H_2O} \qquad (16)$$

oxidizing agents include trivalent, positive iodine compounds,[161] lead tetra-

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[154] German Patent, 642,147.

[155] Cornillot and Alqvier, *Compt. rend.*, 201, 837 (1935).

[156] *J. Org. Chem.*, 1, 163 (1936).

[156a] Office of the Publication Board, Dept. of Commerce, Washington, D. C. (PB-27713, PB-2437, PB-7416).

[157] U. S. Patent, 2,327,066.

[157a] *Synthetic Organic Chemicals* (Eastman Kodak Company), 18, No. 3 (1946).

[158] *J. Am. Chem. Soc.*, 65, 2183 (1943).

[159] *J. Org. Chem.*, 8, 10 (1943).

[160] U. S. Patent, 2,267,375.

[161] German Patent, 717,203.

acetate,[162] and periodic acid.[163] These reagents are highly selective in their action. They have been of the utmost value in analysis and determination of constitution, but they have also made available certain carbonyl compounds not otherwise obtainable. Periodic oxidation especially has been exhaustively reviewed by Jackson.[164] Its usefulness is not limited to glycols, since compounds having a hydroxyl and an amino group (primary or secondary) on adjacent carbon atoms react similarly. Also oxidized are α-ketols, α-diketones, and α-ketoaldehydes.

IX. CARBOXYLIC ACIDS

Two processes for the preparation of carboxylic acids have been intensively studied and technically developed in recent years. They are the oxidation of paraffins, and the reactions of alcohols or olefins with carbon monoxide.

During the past 20 years the Germans have developed the oxidation of paraffins to carboxylic acids extensively and have adapted the process to large scale production.

Numerous comprehensive summaries of the method have appeared.[165] Essentially the process consists in passing paraffin hydrocarbons and air discontinuously, in the vapor phase, at 100° to 150°C., over manganese compounds until the greater portion of the hydrocarbons is oxidized to acids. A large number of the patents in this field is concerned with the separation and purification of the fatty acids of types suitable for soapmaking.

Although industrial interest has been directed chiefly toward fatty acids for soaps, it must not be overlooked that the paraffin oxidation process is also suitable for the preparation of acids containing from 5 to 10 carbon atoms. At present these acids appear in the more volatile fraction when the oxidation products are distilled. However, if the lower hydrocarbons are used, the volatile acids may become the principal products. A start has also been made on the problem of oxidizing paraffin hydrocarbons to alcohols and aldehydes.[166] Furthermore, the formation of hydroxy acids, lactones, ketones, etc. has been observed. A considerable amount of work must yet be done before the oxidation process can be satisfactorily controlled to give each of these products in good yields. However, this will without doubt be done, since the probable rewards are great.

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[162] Criegee, *Angew. Chem.*, 50, 153 (1937); 53, 321 (1940). *Ann.*, 495, 211 (1932); *Ber.*, 64, 260 (1931); 65, 1770 (1932).

[163] Baer, *J. Am. Chem. Soc.*, 62, 1597 (1940).

[164] Jackson, "Periodic Acid Oxidation," in *Organic Reactions*, Wiley, New York, 1944, Vol. II, Chapter 8.

[165] R. Strauss, *Fettchem. Umschau*, 41, 45 (1934). Imhausen, *Chem.-Ztg.*, 62, 213 (1938). Wietzel, *Angew. Chem.*, 51, 531 (1938); 52, 60 (1939). Schrauth, *Chem.-Ztg.*, 63, 274 (1939); Mannes, *Die Chemie*, 57, 6 (1944); *Fette u. Seifen*, 49, 441 (1942). Burstin and Flick, *Chem. Abstracts*, 38 5200 (1944).

[166] U. S. Patents, 1,939,255, 2,265,948, 2,287,125, 2,288,769 and 2,342,028; British Patent, 373,642; French Patent, 714,000.

Oxidation of other materials than saturated hydrocarbons has also been studied extensively. Asinger[167] and Henne and Hill[168] have given detailed instructions for the preparation of acids by ozonolysis of olefins. A group of patents[169] describes the oxidation of alcohols with oxygen in the presence of aldehydes and various metal catalysts. The aldehydes doubtless form peroxides which then oxidize the alcohols. Attention has also been paid to the oxidation of aldehydes[170] and ketones[171] by refined methods. The preparation of dicarboxylic acids for use in making synthetic fibers has been described in a number of patents. Cyclic hydrocarbons,[172] cyclic olefins,[173] cyclic alcohols,[174] and cyclic ketones[175] have been used.

The preparation of carboxylic acids from olefins or alcohols and carbon monoxide has been developed chiefly in this country where olefins are available in large amounts and are cheap, so that their conversion to carboxylic acids is an economical process:

$$CH_2{=}CH_2 + CO + H_2O \longrightarrow CH_3CH_2CO_2H$$

$$RCH_2OH + CO \longrightarrow RCH_2CO_2H$$

In practice, olefins, such as ethylene and butylene, are mixed with water gas and passed in the vapor phase over catalysts at 200° to 400°C. and under high pressures (700 atmospheres or more). A large number of catalysts has been recommended, including hydrogen chloride, chlorides of the alkali metals and of copper or cobalt, oxides of the metals from groups 3 to 6 of the periodic system, phosphates, molybdates,[176] and chlorinated organic acids.[177] Ammonium chloride[178] and carbon tetrachloride adsorbed on charcoal[179] have also been proposed. Halogenated hydrocarbons, such as ethyl chloride, may be used instead of olefins according to Larson.[180] It may be assumed that hydrogen halide is eliminated and an olefin formed under the conditions of the reaction. Hardy[181] uses phosphoric acid as a catalyst and assumes that it also initiates olefin formation.[182] Similar catalysts and conditions have been used to bring about condensations of carbon monoxide and either olefins or alcohols.[183]

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[167] *Ber.*, **75**, 656 (1942).

[168] *J. Am. Chem. Soc.*, **65**, 752 (1943).

[169] U. S. Patents, 2,353,157–2,353,160 and 2,287,803; German Patent, 729,672.

[170] U. S. Patent, 2,294,984; British Patent, 540,915; German Patent, 732,720.

[171] U. S. Patents, 2,267,377 and 2,270,252; British Patent, 540,225.

[172] U. S. Patent, 2,285,601.

[173] U. S. Patent, 2,323,861.

[174] British Patent, 533,066.

[175] U. S. Patents, 2,341,288, and 2,298,387; British Patent, 540,004; German Patent, 725,486.

[176] U. S. Patents, 1,924,762, 1,957,939, 2,008,348 and 2,015,065.

[177] U. S. Patent, 2,025,677.

[178] U. S. Patent, 1,924,765.

[179] U. S. Patent, 2,020,689.

[180] U. S. Patent, 1,993,555.

[181] *J. Chem. Soc.*, **1936**, 364.

A number of methods has been described in recent years for the introduction of the carboxyl group by replacement of other groups. Morton, LeFeure, and Hechenbleicher[184] have studied the reaction of alkyl halides with sodium and carbon dioxide under pressure. Mono- and dicarboxylic acids are formed in varying yields:

$$C_5H_{11}Cl + 2Na + CO_2 \longrightarrow C_5H_{11}CO_2Na + NaCl \qquad (17)$$

$$2C_5H_{11}Cl + 4Na + 2CO_2 \longrightarrow C_4H_9CH(CO_2Na)_2 + C_5H_{12} + 2NaCl \qquad (18)$$

Depending on conditions (pressure, solvent, amount of sodium) either reaction 17 or 18 predominates. The formation of malonic acid derivatives is of especial interest. From 1-chloropentane with sodium and carbon dioxide in ligroin were obtained 51% yields of butylmalonic acid and 40% yields of caproic acid. The well known reaction of CO_2 with Grignard reagents has been found to proceed with good yields from allylic halides.[185]

An interesting procedure has been developed by Arndt and Eistert[186] for converting a carboxylic acid into its next higher homologue. A diazoketone is first prepared by reaction of the acid chloride with diazomethane (Eq. 19). This reactive substance is converted without isolation into the

$$RCOCl + 2CH_2N_2 \longrightarrow RCOCHN_2 + CH_3Cl + N_2 \qquad (19)$$

next higher carboxylic acid or an ester or amide of it by reaction with water, alcohols, ammonia, or amines. The conversion is catalyzed by colloidal silver, copper, or platinum. The synthesis is applicable to aromatic as well as aliphatic acids. Since diazomethane is readily available, the method is valuable for the preparation of various difficultly obtainable acids from their lower homologues. Over-all yields from one acid to the next higher homologue average 50 to 80%. No drastic conditions are employed, and the synthesis is relatively rapid. It is ideal for use on complex or sensitive molecules. Bachmann[187] employed it very successfully in his classical synthesis of the sex hormone, equilenin, and has reviewed it comprehensively.[188] Eistert[189] applied the method to a synthesis of papaverine.

The Hass method for the direct vapor phase nitration of hydrocarbons with nitric acid is described on page 203. The nitro compounds so obtained may be converted directly into carboxylic acids. This reaction which was described first by V. Meyer and Wurster[190] and Geuther[191] has been restudied by Lippincott and Hass.[192] They find that 1-nitropropane when heated with 85% sulfuric acid gives propionic acid in 96% yield along with hydroxylamine sulfate. Sulfuric acid appears to be more effective in the reaction than other acids such as hydrochloric and phosphoric. The mechanisms proposed by various investigators are summarized and discussed by Hass and Riley.[36]

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[182] *J. Chem. Soc.*, **1936,** 358, 362.

[183] U. S. Patents, 1,940,787–1,940,789, 1,946,254–1,946,259, 2,054,807 and 2,068,265.

[184] *J. Am. Chem. Soc.*, **58,** 754 (1936).

[185] Lane, Roberts, and Young, *J. Am. Chem. Soc.*, **66,** 543 (1944).

[186] *Ber.*, **68,** 200 (1935).

[187] Bachmann, Cole, and Wilds, *J. Am. Chem. Soc.*, **62,** 824 (1940).

[188] Bachmann and Struve, "The Arndt-Eistert Synthesis," in *Organic Reactions*, Wiley, New York, 1942, Vol. I, Chapter 2.

[189] *Angew. Chem.*, **54,** 124 (1941).

The reaction of alcohols with alkalies to yield carboxylic acid salts according to Equation 20 has been the subject of several recent publications and patents. This synthesis was discovered by Dumas and Stass.[193] It has been reinvestigated with modern equipment by Weizmann and Garrard[194] and by Reid and co-workers.[195] Reid employed an aqueous-alcoholic solution of alkali and ran the reaction in an autoclave at temperatures above 320°C. The hydrogen evolved created pressures up to 400 atmospheres. The yields were very good. Thus, under suitable conditions ethanol gave sodium acetate in 99% yield. The reaction was also applied to other alcohols but its generality cannot be affirmed without further experimental evidence. A recent patent[196] describes the formation of branched chain acids by heating alcohols and sodium together.

$$RCH_2OH + NaOH \longrightarrow RCO_2Na + 2H_2 \qquad (20)$$

X. CARBONYLATION

A most important series of syntheses with carbon monoxide were developed in Germany during the late war and have only recently[73a,197] been described and made available to scientists generally. Carbon monoxide reacts under pressure (200 atmospheres), at elevated temperature (200–300°C.), and in the presence of carbonyl catalysts (especially nickel or cobalt carbonyls) with a variety of types of organic molecules. For the most part the reactions proceed smoothly and in good to excellent yields.

(*1*) *With acetylenes:*

$$HC{\equiv}CH + CO + H_2O \longrightarrow CH_2{=}CHCO_2H$$

$$HC{\equiv}CH + CO + C_2H_5OH \longrightarrow CH_2{=}CHCO_2C_2H_5 \text{ (yield, 80–90\%)}$$

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[190] *Ber.*, 6, 1168 (1873).
[191] *Ber.*, 7, 1620 (1874).
[192] *Ind. Eng. Chem.*, 31, 118 (1939); U. S. Patents, 2,113,812–2,113,814.
[193] *Ann.*, 35, 129 (1840).
[194] *J. Chem. Soc.*, 117, 324 (1920).
[195] *J. Am. Chem. Soc.*, 61, 99 (1939).
[196] U. S. Patent, 2,293,649.
[197] *Chem. & Met. Eng.*, 53, 120 (1946).

In place of water or alcohols the acetylene and carbon monoxide may react with amines, mercaptans, or acids, to produce amides, thioesters, or anhydrides.

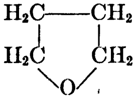
(*2*) *With olefins*:

$$CH_2{=}CH_2 + CO + H_2O \longrightarrow CH_3CH_2CO_2H \ (90\%)$$

$$CH_2{=}CH_2 + CO + CH_3CH_2CO_2H \longrightarrow (CH_3CH_2CO)_2O \ (90\%)$$

$$CH_3CH{=}CHCH_3 + CO + H_2O \longrightarrow$$

$$CH_3CH_2CH(CH_3)CO_2H + CH_3CH_2CH_2CH_2CO_2H$$



$$+ CO + H_2O \longrightarrow HO_2C(CH_2)_4CO_2H \ (70\%)$$

The Oxo reaction described on page 222 is a variation of the reaction of olefins with carbon monoxide.

The possibilities of utilizing the carbonylation reaction in organic synthesis have only been recognized and are far from being completely realized. Preliminary evidence indicates that there are many other interesting applications for catalytic carbonylation reactions.

XI. VINYLATION AND ETHYNYLATION

The reactions of acetylene with itself and with aldehydes, ketones, and organic acids have been known and utilized commercially for a number of years. During the past decade, however, the Germans improved these acetylene reactions and developed new ones, creating thereby a whole series of hitherto rare or unobtainable aliphatic compounds of great promise for both the synthetic laboratory and industry.[198] The work was done under the direction of J. W. Reppe and involved twelve to fourteen years of work by a number of chemists. The results which have only recently been described, may be classified in two groups.

(*1*) *Vinylation.* This includes the reactions of acetylene with alcohols, mercaptans, amines, and acids to form vinyl ethers and thioethers (see section on ethers, page 211), vinyl amines, and vinyl esters. The pressure at which the reactions are run is high enough to prevent boiling of the reactants at the working temperature, 150–200°C. The catalyst is a basic material, usually potassium hydroxide, an alkali metal alcoholate, or a zinc naphthenate. Of particular interest is a new synthesis for acetaldehyde:

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[198] Office of the Publication Board, Dept. of Commerce, Washington, D. C., PB-2437.

$$HC\equiv CH + CH_3OH \longrightarrow H_2C{=}CH{-}O{-}CH_3$$

$$H_2C{=}CH{-}O{-}CH_3 + H_2O \xrightarrow{H^+} CH_3CHO + CH_3OH$$

The methyl alcohol is continuously recycled.

(2) *Ethynylation*—the reaction of acetylene with aldehydes and ketones. By far the most important single discovery is the reaction of acetylene with aqueous formaldehyde giving either 1,4-butynediol or 3-propynol (propargyl alcohol) depending upon conditions. Copper acetylide containing bismuth is used as catalyst.[197]

$$HC\equiv CH + CH_2O \longrightarrow HC\equiv CCH_2OH \quad \text{or} \quad HOCH_2C\equiv CCH_2OH$$

Subsequent reactions of the 1,4-butynediol were extensively studied. (*a*) Hydrogenation gives either 1,4-butenediol or 1,4-butanediol:

$$HOCH_2C\equiv CCH_2OH + H_2 \; - \begin{cases} \xrightarrow{\text{Fe}} HOCH_2CH{=}CHCH_2OH \\ \xrightarrow[\text{Ni-Cu-Cr}]{} HOCH_2CH_2CH_2CH_2OH \end{cases}$$

The 1,4-butenediol may be dehydrated to a dihydrofurane, hydrated to erythritol, or converted to hexamethylenediamine by reaction with hydrogen cyanide and then with hydrogen. (*b*) Hydration with a mercury catalyst followed by dehydration gives vinyl hydroxymethyl ketone (1-hydroxy-3-buten-2-one):

$$HOCH_2C\equiv CCH_2OH \xrightarrow{HgSO_4, H_2O} (HOCH_2COCH_2CH_2OH) \longrightarrow HOCH_2COCH{=}CH_2$$

Similarly 1,4-butanediol was converted into a variety of substances. One of the most interesting of these is γ-butyrolactone, obtained by partial oxidation and lactonization of the diol. For the most complete summary now available on these new products from acetylene the reports[156a] of the Office of the Publication Board of the Department of Commerce should be consulted.

Organic Fluorine Compounds

By WILHELM BOCKEMÜLLER

Translated and revised by CHARLES J. KIBLER

I. RISKS INVOLVED IN WORK WITH FLUORINE AND HYDROGEN FLUORIDE

The technical importance of organic fluorides has steadily increased during the last twenty years. However, our knowledge of the chemistry of these compounds is still meager as compared to that of the other organohalides, because the introduction of fluorine into organic compounds does not proceed as smoothly as does that of chlorine or bromine, and because special apparatus is often required.

Several precautions are necessary when one is working with fluorine and hydrogen fluoride. Although fluorine is a systemic poison, the risk from this is relatively small, because the operator is warned by a characteristic odor somewhat reminiscent of nitric oxide. Much more disturbing is the fact that mixtures of fluorine with organic vapors or gases tend to explode with great violence. Therefore, it is essential that large, closed volumes of fluorine and organic vapors be avoided when fluorine is allowed to react with organic liquids. This is accomplished by passing a finely dispersed stream of fluorine into a vigorously stirred solution or through the use of a suitably built reaction vessel.[1,2] When a gaseous material is to be fluorinated, explosion or total combustion can be avoided by conducting the reaction on the surface of a copper gauze or in a space filled with copper gauze.[3]

Hydrogen fluoride is a frequent source of accidents. The vapor of hot, 40% hydrofluoric acid produces a burn which, with a relatively short exposure, is nearly intolerable. No warning occurs, since the pain does not set in until several hours after the action of the vapor. Concentrated hydrofluoric acid (80%) and anhydrous hydrogen fluoride destroy the skin upon contact. This cauterization by the fluoride ion often leads to a penetrating necrosis which heals very slowly. First aid treatment consists of washing the injured area with a suspension of calcium oxide followed by

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[1] Bockemüller, *Organische Fluorverbindungen*, Enke, Stuttgart, 1936.

[2] Bockemüller, *Ann.*, **506**, 20 (1933).

[3] K. Fredenhagen and Cadenbach, *Ber.*, **67**, 928 (1934). Calfee and Bigelow, *J. Am. Chem. Soc.*, **59**, 2072 (1937).

glycerol-magnesium oxide paste[4] or a magnesium stearate ointment. The injection of a solution of calcium gluconate-lactobionate suppresses the painful necrosis and accelerates the healing process.[4]

II. MATERIALS FOR REACTION VESSELS

Magnesium, copper, stainless steel, and Monel metal equipment have been used successfully in work with fluorine.[1,2,5] Nickel is particularly good, since it becomes coated with a protective fluoride layer and is thus practically unaffected by fluorine even at 750°C.[6] Occasionally glass is used, but this is not recommended. The preparation and storage of compounds such as BrF_3, BrF_5, and ClF_7 have been carried out successfully in vessels of iron, cobalt, nickel, and alloys of these metals.[7] It is claimed that these metals are unharmed at temperatures as high as 127°C. When one is working with concentrated hydrofluoric acid or anhydrous hydrogen fluoride, copper, monel metal, or duraluminum is preferred. Reactions of hydrogen fluoride at higher temperatures are carried out in autoclaves of copper[8] or nickel-lined allegheny metal.[9,10] For the construction of technical apparatus which is exposed at high temperatures to the action of hydrogen fluoride and other fluorides, as well as hydrogen chloride, chrome-nickel steel is suitable.[11] For laboratory work it is best to use platinum or platinum-lined pressure vessels when other mineral acids as well as hydrogen fluoride are present. The industrial progress in the preparation and the handling of inorganic fluorine derivatives will certainly benefit scientific investigations, since both anhydrous hydrogen fluoride and fluorine[6] are now available in cylinders.

III. ADDITION OF FLUORINE TO DOUBLE BONDS

The addition of fluorine to the double bond is possible,[2] but unless the proper precautions are taken the carbon to carbon bond will be ruptured simultaneously. Since the interaction of fluorine with an organic compound liberates a quantity of energy which exceeds the binding energy of the carbon-carbon linkage, a reaction such as the addition of fluorine to ethylene cannot take place by the direct collision of the two substances. When the reaction takes place in solution or on a metal gauze, so that the heat of reaction is quickly dissipated, 2 atoms of fluorine are added to the double bond without excessive decomposition. Thus, in carbon tetrachloride[12] at 0°C., or in difluorodichloromethane at −78°C.,[1,13,14] tetrachloroethylene is converted to *sym*-difluorotetrachloroethane[12,15–17]; the fluorination of tetrachloroethylene in the gaseous phase in contact with copper gauze gives difluorotetrachloroethane as well as other products.[18] Olefins which contain hydrogen also add fluorine. Naturally the yield of the fluorine addition product is diminished by the simultaneous substitution reaction, but the addition of fluorine to the double bond in dilute carbon tetrachloride solution is generally faster than the substitution reaction.[19] When the reaction is carried out in carbon tetrachloride at 0°C., the solvent is slowly attacked by the fluorine. Since pentachlorofluoroethane is one of the products when tetrachloroethylene is fluorinated under these conditions, it is probable that the displaced chlorine adds to the olefin as ClF. Hexadecene adds fluorine to give 1,2-difluorohexadecane; fluorine adds *cis* and *trans* to crotonic acid to give the two stereoisomeric α- and β-difluorobutyric acids; oleic and elaidic acids are changed to the corresponding 9,10-difluorostearic acids.[2] A noteworthy side reaction occurs when an olefin is treated with fluorine. A compound with twice as many carbon atoms as the starting olefin is formed by the combination of 2 olefin molecules to form a new carbon-carbon bond with the simultaneous addition of 2 atoms of fluorine to the ends of this system. When tetrachloroethylene is fluorinated (Eq. 1), about 20% of the starting material is

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[4] K. Fredenhagen and H. Fredenhagen, *Angew. Chem.*, 52, 189 (1939).

[5] Ruff, *Die Chemie des Fluors*, Springer, Berlin, 1920.

[6] von Wartenberg, *Z. anorg. allgem. Chem.*, 242, 406 (1939).

[7] French Patent, 803,855; *Chem. Abstracts*, 31, 2760 (1937).

[8] Simons, Randall, and Archer, *J. Am. Chem. Soc.*, 61, 1795 (1939).

[9] Grosse and Linn, *J. Org. Chem.*, 3, 26 (1938).

[10] Allegheny metal is a chrome-nickel steel with 17 to 20% chromium and 7% nickel.

[11] Kinetic Chemicals Inc., U. S. Patent, 2,058,453; *Chem. Abstracts*, 31, 115 (1937).

$$2Cl_2C{=}CCl_2 + F_2 \longrightarrow FCCl_2CCl_2CCl_2CCl_2F \qquad (1)$$

changed to 1,4-difluorooctachlorobutane.[2,17] A dimerization product was obtained as well as higher polymers in the action of fluorine on crotonic acid.[2]

In most cases it is best to avoid the use of elementary fluorine for the saturation of olefins with fluorine. The use of lead tetrafluoride[20] and iodobenzene difluoride,[21] which are prepared from lead tetraacetate and iodosobenzene, has been suggested by Bockemüller. Recently, a similar reaction was carried out in which the lead tetrafluoride was prepared in the reaction mixture from lead dioxide and hydrogen fluoride.[22] These compounds easily liberate 2 atoms of fluorine which add to active double bonds; *e.g.*, α,α-diphenylethylene is converted to α,β-difluoro-α,α-diphenylethane. 9,10-Anthracene difluoride is formed by the action of tolyl iodofluoride on anthracene and this decomposes to give 9-fluoroanthracene.[23] Traces of hydrogen fluoride or silicon tetrafluoride catalyze the interaction of aryliododifluorides and olefins.

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[12] Fluorine-carbon tetrachloride mixtures are explosive and occasionally ignite spontaneously. Hydrogen fluoride, fluorosulfonic acid, and fluorinated hydrocarbons as well as chlorofluoro derivatives can be used as solvent.

[13] Henne, *J. Am. Chem. Soc.*, **60**, 96 (1938).

[14] Miller, and Bigelow, *J. Am. Chem. Soc.*, **58**, 1585 (1936).

[15] Ruff and Keim, *Z. anorg. allgem. Chem.*, **201**, 245 (1931).

[16] U. S. Patents, 2,013,030 and 2,013,035; *Chem. Abstracts*, **29**, 6900 (1935).

[17] Miller, *J. Am. Chem. Soc.*, **62**, 341 (1940).

[18] Miller, Calfee, and Bigelow, *J. Am. Chem. Soc.*, **59**, 198 (1937).

[19] I. G. Farbenindustrie A.-G., French Patent, 786,123; *Chem. Abstracts*, **30**, 1192 (1936).

[20] Dimroth and Bockemüller, *Ber.*, **64**, 516 (1931).

[21] Bockemüller, *Ber.*, **64**, 522 (1931).

Aromatic fluorides cannot be prepared by direct substitution with fluorine.[17] Any definable products obtained are formed by the addition of fluorine to the aromatic ring, *e.g.*, $C_6Cl_6F_4$ and $C_6Cl_6F_6$ are obtained from hexachlorobenzene and fluorine.[24] Fluorine-containing amorphous materials of high molecular weight are the chief products of the interaction of fluorine and aromatic compounds. They also predominate when lead tetrafluoride and aryliododifluorides are used with aromatic compounds if any reaction occurs. In a few cases definite substitution products are obtained, *e.g.*, *p*-fluorodimethylaniline[21] and fluorobenzanthrone[23] are prepared by the action of aryliodofluoride on the appropriate starting material.

IV. ADDITION OF HYDROGEN FLUORIDE TO DOUBLE BONDS

Hydrogen fluoride adds to double bonds with surprising facility. Although the tendency of hydrogen halides to add to olefins decreases from hydrogen iodide through hydrogen chloride, hydrogen fluoride adds easily to ethylene, propylene, and cyclohexene (Eq. 2). Anhydrous hydrogen

$$CH_2{=}CH_2 + HF \longrightarrow CH_3CH_2F \qquad (2)$$

fluoride[9] is used for this reaction and no catalyst is necessary. With ethylene the addition proceeds best at 90°C., but its homologues react best at 0° or lower, since the concurrent polymerization reaction becomes appreciable at higher temperatures. Hydrogen fluoride adds to propylene in a manner analogous to the addition of the other hydrogen halides, forming isopropyl fluoride. Cyclopropane combines with hydrogen fluoride at 26° to give normal propyl fluoride. Traces of isopropyl fluoride are formed in this reaction as the result of elimination of hydrogen fluoride from the primary product and subsequent recombination. Olefinic acids add hydrogen fluoride in chloroform at 10° or at very gentle heat in a similar manner to yield the corresponding fluoro fatty acids.[25] Thus, fluoroundecylic acid and fluorostearic acid are obtained from undecylenic acid and oleic acid, respectively. In the reaction of oleyl alcohol with hydrogen fluoride, the alcohol group remains intact and fluorostearyl alcohol is formed.[25] Allyl alcohol dissolves in anhydrous hydrogen fluoride with the formation of a red color, but the addition of hydrogen fluoride to the double'bond has not been observed.[26]

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[22] Henne and Waalkes, *J. Am. Chem. Soc.*, **67**, 1639 (1945).

[23] Garvey, Halley, and Allen, *J. Am. Chem. Soc.*, **59**, 1827 (1937).

[24] Bigelow and Pearson, *J. Am. Chem. Soc.*, **56**, 2773 (1934).

[25] I. G. Farbenindustrie A.-G., French Patent, 799,432; *Chem. Abstracts*, **30**, 7585 (1936).

A. Preparation of Ethyl Fluoride

An allegheny metal autoclave with a nickel lining is charged with 200 g. of hydrogen fluoride.[9] The temperature is maintained at 90°C. while 85 g. of ethylene gas are introduced with stirring during 4 hours under a pressure of 20 to 25 atmospheres. The reaction is noticeably exothermic. After the addition of ethylene is complete, stirring and heating are continued for 1 hour. The product is siphoned under pressure into a copper receiver which is cooled with dry ice-acetone mixture to about −80°, and which contains an excess of finely crushed ice to combine with the unchanged hydrogen fluoride. An outlet tube is connected through a soda lime tube to a glass receiver cooled in dry ice-acetone. The contents of the flask are allowed to warm to room temperature; the gaseous fluoride is distilled and recondensed in the glass receiver. A crude product of a purity of 95% is obtained in a yield of 81% of theory (based on the ethylene used). Pure ethyl fluoride boils at −37.7°.

Isopropyl fluoride, b.p. −10.1°C., is obtained in a yield of 61% of theory by the reaction of hydrogen fluoride (8% excess) with propylene at 0°C. for 5 hours.

B. Cyclohexyl Fluoride

In a copper flask fitted with a stirrer, inlet and outlet tube, and cooled externally to −35°C., are placed 200 g. of anhydrous hydrogen fluoride. To this are added dropwise, with continuous stirring during 75 minutes, 400 g. of cyclohexene. The reaction product is immediately poured into a copper beaker containing cracked ice.[27] The cyclohexyl fluoride layer is separated in a separatory funnel, washed with water, and dried with calcium chloride. It is necessary to distil the product under reduced pressure; b.p. 71° to 74.5°C. at 300 mm.; yield 80%.

Cyclohexyl fluoride may also be prepared in a yield of 54% of theory by the reaction of 200 g. of hydrogen fluoride and 740 g. of cyclohexene at 10°C.

The scope of this reaction has not yet been determined. It is a new procedure which offers much promise. The statements in the literature are confusing. Amylene, styrene, indene, and butadiene have been reported to be converted by the action of anhydrous hydrogen fluoride to fluorine-free high polymers,[28] while other ethylenic derivatives such as cinnamic acid are unchanged by hydrogen fluoride.[29] The reaction is reversible; the main problem is to complete the addition reaction and at the same time prevent the formation of resinous products. Increased time of reaction always favors side reactions.[30] By use of a monochloroolefin as starting material, difluoroalkanes of the type RCH_2CF_2R' can be prepared.[31,32]

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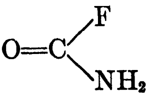
[26] Klatt, *Z. anorg. allgem. Chem.*, 222, 225 (1935).

[27] Caution! Goggles and rubber gloves! Excessive spitting occurs when hydrogen fluoride is mixed with water.

Another reaction of interest is the addition of olefins to aromatic hydrocarbons in the presence of hydrogen fluoride. Benzene reacts with propylene or cyclohexene to give isopropylbenzene or cyclohexylbenzene, respectively, in high yields.[33] The equivalent of a Friedel-Crafts reaction is thus obtained without the presence of aluminum chloride.

Hydrogen fluoride also adds to *alkynes*. Acetylene and hydrogen fluoride react to give a mixture of vinyl fluoride and 1,1-difluoroethane.[34] The claim that mercuric ion[35] is needed as catalyst is apparently unfounded.[30] It is claimed that this reaction can be carried out with anhydrous hydrogen fluoride or with aqueous hydrofluoric acid.[35] The reactions are very violent and uneven. There is a tendency at low temperatures for the reactants to accumulate and then react with explosive force.[30] The addition of anhydrous hydrogen fluoride to homologues of acetylene proceeds, as with olefins, without a catalyst. Thus, 9,10-difluorostearic acid is formed by passing a stream of hydrogen fluoride into a solution of stearolic acid in methylene chloride at 0° to 10°C.[35]

Hydrogen fluoride adds to *ketene* just as other hydrogen halides and gives acetyl fluoride in a quantitative yield.[36] Cyanic acid, in ether solution, adds hydrogen fluoride at a temperature of $-78°C.$ to give carbamyl fluoride:[37]



$$O{=}C\begin{smallmatrix}F\\NH_2\end{smallmatrix}$$

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[28] K. Fredenhagen, *Z. physik. Chem., Abt. A*, **164**, 176 (1933).
[29] Klatt, *Z. physik. Chem., Abt. A*, **222**, 291 (1935).
[30] Henne, in *Organic Reactions*, Wiley, New York, 1944, Vol. II, pp. 49–93.
[31] Renoll, *J. Am. Chem. Soc.*, **64**, 1115 (1942).
[32] Henne and Plueddeman, *J. Am. Chem. Soc*,. **65**, 1271 (1943).
[33] Simons and Archer, *J. Am. Chem. Soc.*, **60**, 2952 (1938).
[34] I. G. Farbenindustrie A.-G., German Patent, 641,878; *Chem. Abstracts*, **31**, 5809 (1937).
[35] I. G. Farbenindustrie A.-G., German Patent, 621,977; *Chem. Abstracts*, **30**, 2314 (1936).
[36] Eschenbach, German Patent, 638,441; *Chem. Abstracts*, **31**, 1042 (1937).
[37] Linhard and Bets, *Ber.*, **73**, 177 (1940).

V. EXCHANGE REACTIONS BETWEEN HALOGENS AND FLUORINE

The interchange of *hydrogen* by fluorine according to Equation 3 is feasible in non-aromatic systems, but there are no important preparations in which this method is used.[2]

$$RH + F_2 \longrightarrow RF + HF \qquad (3)$$

The *replacement* of other *halogens* by fluorine has been successfully carried out in a variety of ways. It is an important means of preparation of aliphatic fluoro derivatives. Elementary fluorine displaces the other halogens in carbon compounds. Although carbon tetrafluoride may be prepared in this way from carbon tetrachloride,[15] this reaction does not have practical mportance. The replacement of a halogen atom is best effected by treatment with any of several inorganic fluorides.

1. Reactions with Hydrogen Fluoride

Hydrogen fluoride converts compounds of the type $RCCl_3$ to RCF_3. The simplest example of this reaction, which proceeds without a catalyst, is the conversion of methyl chloroform stepwise at 150°C. to methyl fluoroform,[38] CH_3CF_3, with the liberation of hydrogen chloride. The reaction (Eq. 4) of benzotrichloride with hydrogen fluoride is of considerable technical importance.[39] The reaction is carried out at 110° under pressure.

$$C_6H_5CCl_3 + HF \longrightarrow C_6H_5CF_3 + 3HCl$$

Derivatives of benzotrichloride are also converted by the action of hydrogen fluoride to the corresponding trifluorides. A trichloromethyl group ortho or para to a chlorine atom does not react. If there are two trichloromethyl groups ortho or para to each other, they are converted simultaneously to trifluoromethyl groups; with mesitylene, the final product is *sym*-$C_6H_3(CF_3)_3$. The polychlorination of *o*-xylene ceases with the formation of *o*-trichloromethylbenzal chloride. When this compound is treated with hydrogen fluoride, all the chlorines are replaced by fluorine.[40] In this isolated case the $-CHCl_2$ group is converted to $-CHF_2$ by the action of hydrogen fluoride. This reaction is not practical with benzal chloride, since a resinous product is usually obtained. The presence of a $-COCl$ group meta or para to a $-CCl_3$ group does not hinder the exchange with hydrogen fluoride; the corresponding trifluoromethylbenzoyl fluoride is formed.[41] o-Trifluoromethylaniline[42] is prepared according to the following scheme:

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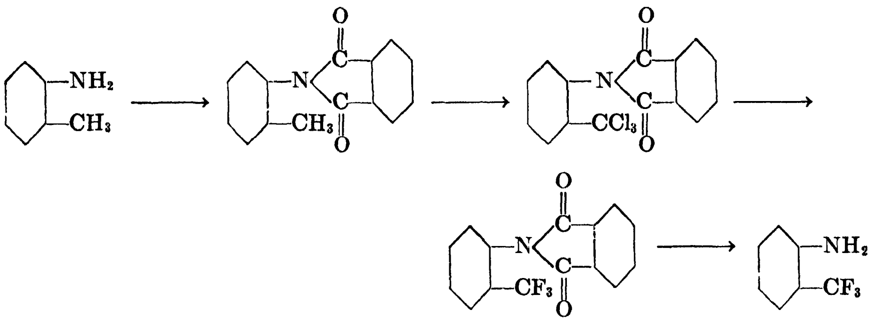
[38] I. G. Farbenindustrie A.-G., German Patent, 670,130; *Chem. Abstracts*, **33**, 2911 (1939).

[39] I. G. Farbenindustrie A.-G., German Patent, 575,593; *Chem. Abstracts*, **27**, 4813 (1933).

[40] This compound can be hydrolyzed with sulfuric acid to *o*-trifluoromethylbenzaldehyde. It can also be chlorinated to *o*-$F_3CC_6H_4CClF_2$ which, by treatment with hydrogen fluoride, gives *o*-$F_3CC_6H_4CF_3$.



When the trichloromethyl group is bound to sulfur, as in trichloromethylphenyl sulfide, all the chlorine atoms are exchanged[43] (Eq. 4). The

$$C_6H_5SCCl_3 + 3HF \longrightarrow C_6H_5SCF_3 + 3HCl \qquad (4)$$

presence of substituents such as chlorine, methyl, nitro, and carboxyl in the benzene ring does not influence this reaction.

Preparation of Benzotrifluoride

A copper flask is fitted with a copper stirrer, a copper inlet tube which extends to the bottom of the flask, and another copper tube for the exit gases.[39,44] The flask is charged with 500 g. of benzotrichloride and the temperature maintained at 0°C. while 200 g. of hydrogen fluoride are admitted slowly and continuously with stirring and cooling during the course of 72 hours. The exit gas consists mainly of hydrogen chloride with some hydrogen fluoride and small amounts of benzotrifluoride. As the reaction nears completion, the concentration of hydrogen fluoride and the desired product increases, and they should be collected in a copper trap immersed in an ice-salt bath. The exit gas may be analyzed qualitatively for hydrogen chloride and hydrogen fluoride, and the relative amounts estimated by testing with beads of aqueous solutions of silver nitrate and calcium chloride held in a nichrome wire. Although the reaction can be carried to 95% completion, the concentration of hydrogen fluoride in the exit gas rises at about 70% completion, and it is economical to stop at this point. When the reaction is stopped, the mixture is allowed to warm to room temperature, and a small amount of sodium fluoride is added to remove the excess hydrogen fluoride. After standing a short time, with occasional shaking, it is filtered and the filtrate is distilled. The yield of benzotrifluoride, b.p. 103°C., is 300 g. The distillation tailings contain chlorofluorides and may be reworked in subsequent operations.

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[41] I. G. Farbenindustrie A.-G., British Patent, 465,885; *Chem. Abstracts*, **31**, 7667 (1937). I. G. Farbenindustrie A.-G., French Patent, 820,795; *Chem. Abstracts*, **32**, 3422 (1938).

[42] I. G. Farbenindustrie A.-G., French Patent, 805,704; *Chem. Abstracts*, **31**, 4342 (1937).

[43] I. G. Farbenindustrie A.-G., French Patent, 820,796; *Chem. Abstracts*, **32**, 3422 (1938).

[44] Simons and Lewis, *J. Am. Chem. Soc.*, **60**, 492 (1936).

The replacement of chlorine by fluorine through the use of hydrogen fluoride is limited, except in a few cases, to organic compounds such as benzotrichloride which has 3 chlorine atoms bound to 1 carbon atom. Ethylidene chloride[45] and acyl chlorides[39,46] will react under the appropriate conditions with hydrogen fluoride to give the corresponding fluorides. Carbon tetrachloride, chloroform, and hexachloroethane are not converted into their fluoro derivatives in this way. An important modification of the reaction was made by Swarts, who discovered that traces of pentavalent antimony catalyzed the reaction of organic halides with either hydrogen fluoride or antimony trifluoride. Compounds which contain at least 2 chlorine or bromine atoms bound to a carbon atom exchange their halogen atoms under these conditions. Swarts recommended the addition of about 5% of bromine or antimony pentafluoride. At the present time chlorine is generally added to the amount required for the particular reaction. In many cases the reaction occurs with antimony trifluoride alone as for example with benzotrifluoride. This reaction (Eq. 5) proceeds through the

$$C_6H_5CCl_3 + SbF_3 \longrightarrow C_6H_5CF_3 + SbCl_3 \tag{5}$$

intermediates $C_6H_5CCl_2F$ and $C_6H_5CClF_2$, which are easily converted to benzotrifluoride. If it is carried out at room temperature with an excess of benzotrichloride, the chief product is $C_6H_5CClF_2$[47] which is contaminated with a little $C_6H_5CCl_2F$. The presence of chlorine in the nucleus does not affect the reaction. However, *o*-fluorobenzotrichloride is not successfully converted to *o*-fluorobenzotrifluoride by this method,[48] while the reaction proceeds normally with the para isomer. The presence of a meta nitro group does not hinder the reaction. The 3 chlorine atoms in 1,1,1′-trichlorodimethyl ether are replaced easily by fluorine by heating with excess antimony trifluoride.[49] Acyl chlorides are converted to the corresponding fluorides by the action of antimony trifluoride as well as by hydrogen fluoride.

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[45] I. G. Farbenindustrie A.-G., German Patent, 670,130; *Chem. Abstracts*, **33,** 2911 (1939).

[46] Kinetic Chemicals Inc., U. S. Patent, 2,062,743; *Chem. Abstracts*, **31,** 700 (1937).

[47] Swarts, *Bull. classe sci. Acad. roy. Belg.*, 2, 414 (1900); *Chem. Zentr.*, **1900, II,** 667.

[48] Booth, Elsey, and Burchfield, *J. Am. Chem. Soc.*, **57,** 2066 (1935).

[49] Booth and Burchfield, *J. Am. Chem. Soc.*, **57,** 2070 (1935).

2. Reactions with Antimony Trifluoride

A. Preparation of *p*-Chlorobenzotrifluoride

215 g. of *p*-chlorobenzotrichloride are mixed with 200 g. (excess) of sublimed antimony trifluoride in a glass distilling flask and the mixture is heated rapidly to initiate the reaction. The reaction proceeds rapidly and smoothly.[48] The product is washed several times with 6 *N* hydrochloric acid, followed by several washings with water. It is dried over barium oxide and distilled, b.p. 139°C.; yield 148 g. (95%).

Pure antimony trifluoride does not have broad utility as such, but, in conjunction with pentavalent antimony salts, it forms a very important means of fluorine exchange. As mentioned above, a common method of obtaining the desired amount of pentavalent antimony is to add chlorine or bromine in a quantity ranging from 5 to 100 mole per cent. Swarts considered the resulting pentavalent salt to be a mixed halide of the type SbF_3Cl_2, but Ruff represents it as a double salt, $SbF_5 \cdot SbCl_5$. The reaction velocity of halogen exchange may be controlled by suitable additions of catalyst as $SbCl_5$, Br_2, or Cl_2. It is not necessary to use pure antimony pentafluoride.

An equal molecular mixture of antimony trifluoride and bromine reacts with carbon tetrachloride at 45° to 50°C. to give $CFCl_3$[50,51] which distils at 24.9°. If this reaction is carried out at 100°C. in an autoclave, the main product is dichlorodifluoromethane. This product, which is the commercial refrigerant Freon 12, is obtained in a yield of 70% with the addition of relatively small amounts of catalyst.[52] Chlorotrifluoromethane occurs as a by-product, but tetrafluoromethane is not formed. Dichlorofluoromethane and chlorodifluoromethane are prepared from chloroform in an analogous manner.[53,54] The fluorination of bromoform with antimony trifluoride as catalyst, also stops at the formation of CHF_2Br.[55] Methylene chloride is converted to CH_2FCl and CH_2F_2,[54] but homologues of the type $RCHCl_2$ decompose under these conditions. Compounds of this type can be fluorinated with mercurous fluoride. On the other hand, aliphatic compounds of the type RCF_2R' are prepared very successfully by the antimony trifluoride method. The intermediate, $RCClFR'$, is also formed. Benzophenone difluoride is prepared in this way from benzophenone dichloride.[56]

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[50] Swarts, *Ber.*, 26, 681 (1893).
[51] Swarts, *Bull. classe sci. Acad. roy. Belg.*, 24, 309 (1893).
[52] Midgley and Henne, *Ind. Eng. Chem.*, 22, 542 (1930).
[53] Booth and Bixby, *Ind. Eng. Chem.*, 24, 637 (1932).
[54] Henne, *J. Am. Chem. Soc.*, 59, 1400 (1937).
[55] Henne, *J. Am. Chem., Soc.*, 59, 1200 (1937).
[56] Henne and Leicester, *J. Am. Chem. Soc.*, 60, 864 (1938).

B. Preparation of 2,2-Difluoropropane

2,2-Dichloropropane cooled to 0°C. is added to a 25% excess of antimony trifluoride containing 5% of bromine by weight, also cooled to 0°.[57] The glass reaction vessel is connected to a metal reflux condenser which is cooled with ice. The reaction starts promptly and is regulated by means of an ice bath intermittently applied. At the end of the operation, the reaction vessel is heated to about 70°. The vapors passing through the condenser are caught in a water gasometer, or in a receiver cooled with solid carbon dioxide. This operation, quickly performed, yields about 85% of 2,2-difluoropropane, b.p. −0.6° to −0.2°C., and 10 to 15% of 2-chloro-2-fluoropropane, b.p. 35.2°C.

A selection of the aliphatic compounds that are obtained from the corresponding chloro derivative by the antimony trifluoride method is shown in Table I. Besides providing a summary, Table I illustrates the course and extent of the reaction. The —CCl_3 group reacts most easily. The —$CHCl_2$ group, if bound to —CCl_2—, is slow to react, while the —CHCl— group is not usually converted to —CHF— under these conditions. In the system —CCl_2CCl_3 both groups are attacked; the —CCl_3 group is first converted stepwise to —$CClF_2$, and then the adjacent group is converted to —CClF—. Subsequent substitution may occur in either group but only one of the remaining halogens is replaced and that with great difficulty. In contrast to this, if the group —CCl_2— is bound to carbon atoms which

TABLE I

CCl_4[58]
CCl_3F
CCl_2F_2
$CClF_3$

$CHCl_3$[58]
$CHCl_2F$
$CHClF_2$

CH_2Cl_2[54]
CH_2ClF
CH_2F_2

$H_3C—CCl_2—C_2H_5$[59]
$H_3C—CF_2—C_2H_5$

$H_3C—CCl_3$[60]
$H_3C—CCl_2F$
$H_3C—CClF_2$
$H_3C—CF_3$

$Cl_3C—CCl_3$[61,62]
$Cl_3C—CCl_2F$
$FCl_2C—CCl_2F$
$FCl_2C—CClF_2$
$F_2ClC—CClF_2$

$HCl_2C—CHCl_2$[63]
$HCl_2C—CHClF$
$HCl_2C—CHF_2$

$HCl_2C—CCl_3$[64]
$HCl_2C—CCl_2F$
$HCl_2C—CClF_2$
$HClFC—CClF_2$
$HF_2C—CClF_2$

$HCl_2C—CCl_2—CCl_3$[65]
$HCl_2C—CCl_2—CClF_2$
$HCl_2C—CClF—CClF_2$
$HCl_2C—CClF—CF_3$

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[57] Henne and Renoll, *J. Am. Chem. Soc.*, **59**, 2434 (1937).
[58] Frigidaire Corp., French Patent, 701,324; *Chem. Abstracts*, **25**, 4011 (1931).
[59] Henne, Renoll, and Leicester, *J. Am. Chem. Soc.*, **61**, 938 (1939).
[60] Henne and Renoll, *J. Am. Chem. Soc.*, **58**, 889 (1936).
[61] Locke, Brode, and Henne, *J. Am. Chem. Soc.*, **56**, 1726 (1934).
[62] Booth, Mong, and Burchfield, *Ind. Eng. Chem.*, **24**, 328 (1932).
[63] Swarts, *Mém. Couronnés Acad. roy. Belg.*, **61**, 1-94 (1901).
[64] Henne and Ladd, *J. Am. Chem. Soc.*, **58**, 402 (1936).
[65] Henne and Renoll, *J. Am. Chem. Soc.*, **61**, 2489 (1939).

contain only hydrogen atoms, it is easily converted to —CClF— or —CF_2—. Monohalogenoalkanes and compounds which contain 1 or more halogen atoms bound to an unsaturated carbon atom, such as tetrachloroethylene, are not changed to the corresponding fluoro derivative by the action of antimony trifluoride.

As a result of the use of dichlorodifluoro derivatives of the lower paraffins as refrigerants in mechanical refrigerators and air conditioning units, the patent literature of this class of compounds is extensive. Their physiological inertness is extremely valuable when leakage of the refrigerant might cause serious damage if it were toxic. Antimony trichloride, like most other inorganic halides, is converted to antimony trifluoride[66] by the action of hydrogen fluoride. Thus reaction 6 may be carried out with relatively small amounts of antimony trichloride (and traces of pentavalent antimony), since antimony trifluoride is continuously regenerated by the hydrogen fluoride present.[11,67,68] Chromium salts[46,69,70] may also be used for this reaction.

$$CCl_4 + 2HF \longrightarrow CCl_2F_2 + 2HCl \qquad (6)$$

When antimony pentachloride is used as catalyst, it not only effects the replacement of chlorine atoms, but may cause the simultaneous substitution of hydrogen or the addition of chlorine to an olefin, the catalyst being reduced to antimony trichloride. The chlorine atoms thus introduced can be replaced subsequently by fluorine.[46,70,71]

Although it is necessary to have at least 2 chlorine atoms attached to 1 carbon atom of an alkane derivative before it is possible to use hydrogen fluoride or antimony trifluoride for the exchange reaction, acyl chlorides are easily changed to acyl fluorides by these reagents. Reaction 7 proceeds quantitatively by dissolving the acyl chloride in anhydrous hydrogen fluoride. Hydrogen chloride is evolved owing to its nearly complete insolubility in hydrogen fluoride. This method[46,72] is important for the preparation of the higher boiling acyl fluorides which are easily separated from the hydrogen fluoride by distillation. Acyl fluorides may be prepared also by the use of antimony trifluoride. The yield of acetyl fluoride obtained by

$$RCOCl + HF \longrightarrow RCOF + HCl \qquad (7)$$

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[66] General Motors Corp., U. S. Patent, 2,024,008; *Chem. Abstracts*, **30**, 1191 (1936).

[67] Kinetic Chemicals Inc., German Patent, 552,919; *Chem. Abstracts*, **26**, 5967 (1932).

[68] Kinetic Chemicals Inc., U. S. Patent, 2,024,095; *Chem. Abstracts*, **30**, 1067 (1936).

[69] Imperial Chemical Industries, U. S. Patent, 2,110,369; *Chem. Abstracts*, **32**, 3422 (1938).

[70] Kinetic Chemicals Inc., U. S. Patent, 2,005,710; *Chem. Abstracts*, **29**, 5123 (1935).

[71] Imperial Chemical Industries, British Patent, 454,577; *Chem. Abstracts*, **31**, 1045 (1937).

[72] K. Fredenhagen and Cadenback, *Z. physik. Chem., Abt. A*, **164**, 201 (1933).

this method is poor, but benzoyl fluoride may be prepared in a yield of 77% of theory.[73] In the latter case, some benzoylbenzoyl fluoride is obtained as the result of a Friedel-Crafts type condensation. Benzoyl fluoride may also be prepared in good yield (80%) by the action of KHF_2 on benzoyl chloride.[74] Potassium fluoride and acetyl chloride react in acetic acid to give acetyl fluoride. As illustrated by Equations 8, acetyl fluoride can be

$$\begin{gathered} CH_3CO_2H + C_6H_5COCl \longrightarrow CH_3COCl + C_6H_5CO_2H \\ CH_3COCl + KF \longrightarrow CH_3COF + KCl \end{gathered} \tag{8}$$

prepared by the action of potassium fluoride on a solution of benzoyl chloride in acetic acid. The most volatile component, acetyl fluoride, is removed by distillation as it is formed.[75] This method is also used successfully for the preparation of formyl fluoride.

Sulfonyl fluorides can be obtained by warming the sulfonyl chloride with zinc fluoride.[76] Since the sulfonyl fluorides are not easily hydrolyzed, aliphatic[76] or aromatic[77] sulfonyl fluorides may be prepared smoothly by the action of an aqueous potassium fluoride solution on the corresponding sulfonyl chloride.

The increased reactivity of the chlorine atom in 1-chloro-2,4-dinitrobenzene permits replacement of the halogen by fluorine simply by heating the compound with potassium fluoride in nitrobenzene.[78] Picryl fluoride is prepared in a similar manner.[79]

3. Reactions with Silver Fluoride

Silver fluoride[80] is used to replace the other halogens in alkyl halides.

$$RX + AgF \longrightarrow RF + AgX$$

The silver fluoride can be used in solution or as a fine powder mixed with calcium fluoride.[2,81] This powder is prepared by stirring 2 parts of silver carbonate and 4 parts of calcium fluoride with 1 part of 40% hydrofluoric acid. The resulting paste is dried at 100°C., and finally at 140° and ground to a fine powder. It is essential to dry the silver fluoride thoroughly before use, since it is very hygroscopic, and it must be completely dry before consistent results can be obtained. Acetonitrile[82] and anhydrous hydrogen fluoride[83] are the best solvents to use if it is desired to carry out the reaction in solution.

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[73] Vosnesenskii, *J. Gen. Chem.*, 9, 2148 (1939); *Chem. Abstracts*, 34, 4053 (1940).

[74] Tseng and Mai, *J. Chinese Chem. Soc.*, 4, 22 (1936); *Chem. Abstracts*, 30, 2943 (1936).

[75] Nessmejenow and Kahn, *Chem. Zentr.*, 1936, I, 4287–4288.

[76] Davies and Dick, *J. Chem. Soc.*, 1932, 483, 2042.

[77] Davies and Dick, *J. Chem. Soc.*, 1931, 2104.

[78] Gottlieb, *J. Am. Chem. Soc.*, 58, 532 (1936).

[79] Leonhard, U. S. Patent, 2,179,605; *Chem. Abstracts*, 34, 1852 (1940).

[80] For the preparation of silver fluoride see footnote 5.

[81] Ruff, *Ber.*, 69, 299 (1936).

[82] Helferich and Gootz, *Ber.*, 62, 2505 (1929).

Silver fluoride has the disadvantage that only half of the fluorine is available, because the exchange reaction stops with the formation of the addition compound AgF—AgX. Therefore 2 equivalents of silver fluoride must be used. In the reaction of higher alkyl bromides, an olefin is obtained occasionally by the elimination of hydrogen bromide. The formation of this olefin accounts for the fact that *sec*-butyl fluoride as well as *n*-butyl fluoride is obtained by the action of silver fluoride on *n*-butyl bromide.[84,85] The presence of the olefin also explains the origin of a monofluoro derivative containing twice as many carbons as the starting material, *e.g.*, decyl fluoride from *n*-amyl bromide.[86]

4. Reactions with Mercurous Fluoride

Mercurous fluoride[87] can be used advantageously in place of silver fluoride. To be useful, mercurous fluoride, like silver fluoride, must be pure and dry. Alkyl iodides are converted to the corresponding fluorides in good yields by this method. Alkyl bromides may be used but the yields are poor, while alkyl chlorides are not at all suitable. Mercurous fluoride reacts with iodoform, replacing all the iodine atoms to give fluoroform contaminated with small amounts of $CHFI_2$ and CHF_2I.[81] When ethylene bromide and ethylidene bromide are treated with mercurous fluoride, hydrogen bromide is eliminated and vinyl bromide is obtained; other polyhalogenated paraffin derivatives behave similarly.

Preparation of Fluoroform

A mixture of 33.4 parts of mercurous fluoride, 20 parts of iodoform, and 40 parts of calcium fluoride is triturated in a suitable flask, and heated by means of a bath to 20°C.[81] The reaction begins at this point, and the temperature of the mixture rises spontaneously to 150°C. The product is condensed in a liquid air trap. On redistillation, pure fluoroform is obtained in a yield of 45% of theory; b.p. −84.4°C. The residue from the distillation consists of CHF_2I and $CHFI_2$.

5. Reactions with Mercuric Fluoride

Mercuric fluoride is one of the best reagents for the replacement of bromine or iodine by fluorine. The chief drawback is the difficulty encountered in its preparation. Silver fluoride and mercurous fluoride may be prepared in aqueous solution, but the only satisfactory method of making mercuric fluoride is by the action of hydrogen fluoride on mercuric chloride.[88] When mercuric fluoride comes in contact with water, the inactive dihydrate, $HgF_2 \cdot 2H_2O$, is formed from which water cannot be removed. The reaction of mercuric fluoride with alkyl halides, which proceeds according to Equation 9,[88] occurs more easily than with mercurous fluoride.

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[83] K. Fredenhagen, *Z. Elektrochem.*, 37, 684 (1931).

[84] Desreux, *Bull. classe sci. Acad. roy. Belg.*, 20, 457 (1934); *Chem. Abstracts*, 28, 5805 (1934).

[85] Desreux, *Bull. soc. chim. Belg.*, 44, 1 (1935); *Chem. Abstracts*, 29, 2505 (1935).

[86] Swarts, *Bull. soc. chim.*, 35, 1533 (1924); *Bull. soc. chim. Belg.*, 30, 302 (1921).

[87] For preparation of mercurous fluoride see Henne and Renoll, *J. Am. Chem. Soc.*, 60, 1060 (1938).

$$2RX + HgF_2 \longrightarrow 2RF + HgX_2 \qquad (9)$$

The reaction with the lower alkyl bromides or iodides is brisk but easily controlled, and the corresponding fluorides are obtained in nearly quantitative yields.

Alkyl chlorides react much more slowly. Mercuric fluoride is clearly superior to mercurous fluoride as a reagent for converting ethylene bromide or ethylidene bromide to the corresponding fluorides. The chief products are $BrCH_2CH_2F$ and CH_3CHF_2, respectively, mixed with small amounts of FCH_2CH_2F and CH_3CHBrF; butadiene and butyl fluoride are also by-products in these reactions. Acetylene tetrabromide is converted stepwise to acetylene tetrafluoride. Methylene chloride and chloroform do not react with mercuric fluoride at ordinary temperatures, and, therefore, can be used as solvents. Alcohols, esters and ethers cannot be used as solvents, because they prevent the reaction.

A convenient substitute for mercuric fluoride has been introduced by Henne and co-workers.[59,89] Mercuric oxide is treated with hydrogen fluoride at room temperature in the presence of the compound to be fluorinated. The mercuric fluoride or its monohydrate, in the nascent state, reacts with a large number of organohalides. The general procedure is quite simple.

Red mercuric oxide is added to either a pure liquid organohalide, or to a solution of the organohalide, contained in a nickel flask. The mixture is well stirred to prevent the formation of a heavy paste or lumps. The reaction flask is cooled externally, and dry hydrogen fluoride is passed in at such a rate as to maintain the desired temperature. The red color of the mercuric oxide gradually becomes lighter, and finally becomes pure white; this is the end of the reaction. The optimum temperature varies from −20° to +50°C., and the yields by this method are generally high. Methylene chloride and chloroform, which do not react with pure mercuric fluoride, are converted to methylene fluoride and chlorodifluoromethane, respectively. The following groups are converted to the corresponding fluoro derivatives: $—CH_2Br$, $—CHCl_2$, and $RCCl_2R$. The troublesome splitting of halogen halide to form olefins does not occur when this method is used.

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[88] Henne and Midgley, *J. Am. Chem. Soc.*, 58, 884 (1936).

[89] Henne, *J. Am. Chem. Soc.*, 60, 1569 (1938).

This reagent can also be employed to replace halogens in organic esters, although, as pointed out above, pure mercuric fluoride cannot be used successfully in the presence of esters.

The reactivity of the easily accessible mercurous fluoride can be increased by the addition of iodine.[90,91] Iodine reacts with mercurous fluoride according to Equation 10, producing the reactive mercuric fluoride.

$$2HgF + I_2 \longrightarrow HgF_2 + HgI_2 \qquad (10)$$

While mercurous fluoride does not react appreciably with boiling methyl iodide, when iodine is added, methyl fluoride is obtained in excellent yield. The reaction is carried out by adding the calculated amount of mercurous fluoride slowly to a solution of iodine in excess methyl iodide, or by treating a suspension of the mercurous fluoride in methyl iodide with iodine. This method permits the replacement by fluorine of the halides when more than one are bound to a carbon atom. Methylene fluoride is obtained from methylene iodide, ethylidene fluoride from ethylidene bromide, as well as dibromodifluoroethane from tetrabromoethane.[87] The same products are obtained by the use of this reagent as are obtained with mercuric fluoride, but the yields are somewhat smaller and the procedure more troublesome.

When mercurous fluoride is treated with chlorine in a steel autoclave,[87] mercuric chlorofluoride or a mixture of mercuric fluoride and mercuric chloride is obtained. This reacts with ethylene bromide to give $BrCH_2$-CH_2F and FCH_2CH_2F. A small amount of $BrCH_2CH_2Cl$ is also obtained.[87]

In many cases in which a sufficiently reactive halogen atom is present, this halogen atom can be replaced by fluorine with thallous fluoride. Alkyl chlorocarbonates,[92] iodoacetone,[93] bromoacetone,[94] ethyl bromoacetate,[95] and benzyl bromide[95] are converted to the corresponding fluorides by heating in ether with thallous fluoride.

The conversion of alcohols to fluorides (Eq. 11) has not obtained prepar-

$$ROH + HF \longrightarrow RF + H_2O \qquad (11)$$

ative importance. This reaction proceeds much more slowly than the corresponding exchange reaction involving the other halogens. Ethyl fluoride is obtained from absolute ethanol and anhydrous hydrogen fluoride by heating at 140°C. in a sealed tube.[96] The reaction can be accelerated by the

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[90] Swarts, *Bull. classe sci. Acad. roy. Belg.*, 22, 781 (1936); *Chem. Ab.*, 30, 4153 (1936).

[91] Swarts, *Bull. soc. chim. Belg.*, 46, 10 (1937); *Chem. Abstracts*, 31, 7393 (1937).

[92] Goswami and Sarkar, *J. Indian Chem. Soc.*, 10, 537 (1933).

[93] P. C. Rây, Sarkar, and A. Rây, *Nature*, 132, 749 (1933); *Chem. Abs.*, 28, 1015 (1934).

[94] P. C. Rây, Goswami, and A. C. Rây, *J. Indian. Chem. Soc.*, 12, 93 (1935).

[95] P. C. Rây and A. C. Rây, *J. Indian Chem. Soc.*, 13, 427 (1936); *Chem. Abstracts*, 30, 8144 (1936).

[96] Meslans, *Ann. chim.*, 7, 94 (1896).

use of catalysts,[97] but no industrial application of this is known. The tendency of anhydrous beryllium fluoride[98,99] to form the oxyfluoride can be utilized to effect this exchange. The reaction is carried out in excess hydrogen fluoride or in the presence of $NaHF_2$ (Eq. 12). When $NaHF_2$ is used, Na_2BeF_4, as well as basic beryllium fluoride, is one of the products.

$$RCH_2OH + 2BeF_2 \longrightarrow RCH_2F + BeO \cdot BeF_2 + HF \qquad (12)$$

VI. USE OF DIAZONIUM SALTS FOR INTRODUCTION OF FLUORINE INTO AROMATIC COMPOUNDS

Aromatic fluorides are nearly always prepared from the diazotized amines. It was shown in 1886 that fluorobenzene can be prepared from aniline in a yield of 20% of theory.[100,101] A copper catalyst is used in this reaction, but the use of a copper catalyst in analogous reactions has been harmful.[102] The yield of fluorobenzene may be increased by the use of concentrated (50 to 70%) hydrofluoric acid.[102] This method has been displaced by two other methods; namely, diazotization and decomposition of the diazonium fluoride in anhydrous hydrogen fluoride,[103] and the preparation of the insoluble diazonium fluoborate[104] and subsequent decomposition of the dried salt.

1. Preparation of Fluorobenzene

In an iron container fitted with a stirrer and condenser are placed 500 g. of aniline, and 1000 g. of hydrogen fluoride are added with cooling.[103] To this are added during the course of 1 hour, 430 g. of dry sodium nitrite. The temperature is maintained at about 5°C. The reaction mixture is then heated to 30° to 40°. The velocity of the evolution of nitrogen can be controlled easily by regulating the temperature. A reflux condenser is used to diminish the loss of fluorobenzene. The reaction mixture consists of a mixture of fluorobenzene, hydrogen fluoride, and sodium fluoride. The yield of fluorobenzene, b.p. 85° to 86°C., is 450 g. (84% of theory).

The *fluoborate* method for preparing aromatic fluorides was developed by Balz and Schiemann.[104,105] The dried diazonium fluoborate decomposes according to Equation 13. The diazonium fluoroborates, in contrast

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[97] Scherer, *Angew. Chem.*, **52**, 457 (1939).

[98] S. A. Processi Privative Industriali, Italian Patent, 343,035; *Chem. Zentr.* **1937, II**, 2432.

[99] Italian Patent, 350,412; *Chem. Zentr.*, **1939, II**, 1735.

[100] Wallach, *Ann.*, **235**, 255 (1886).

[101] Wallach and Hensler, *Ann.*, **243**, 219 (1888).

[102] Swarts, *Bull. classe sci. Acad. roy. Belg.*, **1913**, 241; *Chem. Abs.*, **7**, 1703 (1913).

[103] I. G. Farbenindustrie A.-G., German Patent, 600,706; *Friedl.*, **21**, 315; *Chem. Abstracts*, **28**, 7260 (1934).

[104] Balz and Schiemann, *Ber.*, **60**, 1186 (1927).

[105] Schiemann, *J. prakt. Chem.*, **140**, 97 (1934).

$$C_6H_5N_2BF_4 \longrightarrow C_6H_5F + N_2 + BF_3 \qquad (13)$$

to most diazonium salts, are relatively insoluble. They are precipitated by the addition of fluoboric acid or sodium fluoborate to an aqueous solution of the diazonium chloride. Aromatic amino acids and aminophenols, because of the high solubilities of their diazonium fluoborates, are converted first to esters or methoxy derivatives. Then the resulting fluoro derivative can be hydrolyzed or demethylated by standard methods. An important property of diazonium fluoroborates is their stability to shock and percussion. They do not explode when heated, but are decomposed smoothly. However, the decomposition of nitrobenzene diazonium fluoborate can become violent, and is best carried out by admixture with an inert material such as sand, soda, or alkali fluoborate. The decomposition can be carried out also under diminished pressure.[106]

The yields from this method depend on two factors: first, on the solubility of the diazonium fluoborate; and second, on the course of the thermal decomposition of the fluoroborate. A brief summary is given in Table II, which is an extract of the compilation by Schiemann.[104,105] The yield of diazonium fluoborate is given in Column A, and the yield of fluoride, based on the fluoborate, is given in Column B.

TABLE II

Compound	Diazonium fluoborate (A)	Fluoride, % (B)	Compound	Diazonium fluoborate (A)	Fluoride, % (B)
Fluorobenzene	70	80	*p*-Fluorobromobenzene	64	75
o-Fluorotoluene	82	90	*o*-Fluoronitrobenzene	74	18
m-Fluorotoluene	76	87	*p*-Fluoronitrobenzene	96	47
p-Fluorotoluene	67	97	*p*-Fluorodimethylaniline	56	17
α-Fluoronaphthalene	91	98	*o*-Fluoroanisole	52	67
β-Fluoronaphthalene	90	69	*m*-Fluoroanisole	82	64
p-Fluorobiphenyl	88	85	*p*-Fluoroanisole	85	67
o-Difluorobenzene	45	30	Ethyl *p*-fluorobenzoate	96	89
p-Difluorobenzene	63	61			

Schiemann also applied this procedure with success to tetrazotized diamines, thereby introducing 2 atoms of fluorine into the molecule in one step. Column A of Table III gives the yield of tetrazonium fluoborate, while Column B gives the yield of difluoro derivative.

The Schiemann fluoborate process is excellent for laboratory use not only because of its wide range or application, but also because no special apparatus is necessary. The preparation of diazonium fluoborates can be carried out in a paraffin-lined flask, and the thermal decomposition can be

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[106] Kleiderer and Adams, *J. Am. Chem. Soc.*, **53**, 1577 (1931).

TABLE III

Compound	Tetrazonium fluoborate % (A)	Difluoro derivative % (B)	Compound	Tetrazonium fluoborate % (A)	Difluoro derivative % (B)
m-Difluorobenzene	88	44	2,2′-Difluorodiphenyl	84	70
p-Difluorobenzene	82	33	3,3′-Difluorodiphenyl	98	50
1,5-Difluoronaphthalene	92	54	4,4′-Difluorodiphenyl	95	85

conducted in ordinary glass apparatus. Also, the costs of the inorganic materials, aqueous hydrofluoric acid and boric acid, are small.

2. Preparation of Fluorobenzoic Acid

In a 5 liter round bottomed flask are placed 165 g. (1 mole) of ethyl *p*-aminobenzoate, 300 cc. of water, and 204 cc. (2.5 moles) of concentrated hydrochloric acid (sp.gr. 1.19).[107] This mixture is warmed on a steam bath for 1 hour with occasional shaking. The flask containing the resulting white paste of *p*-carbethoxyaniline hydrochloride is placed in an ice-salt bath and cooled to 0°C. The mixture is stirred mechanically, and a solution of 72.6 g. (1 mole) of 95% sodium nitrite in a minimum quantity of water is run in slowly while the temperature is kept below 7°. The diazotization is complete when a faint positive test for nitrous acid with starch-iodide paper persists for 10 minutes.

68 g. (1.1 moles) of boric acid are dissolved in 133 g. (4 moles) of 60% hydrofluoric acid in a lead jar or a beaker coated with paraffin wax. If the latter is used, it is necessary to keep the temperature below 25°C. to avoid melting the paraffin wax.

The ice-cold fluoboric acid solution is added rather rapidly, with stirring, to the diazonium solution while the temperature is kept below 10°C. A thick paste of *p*-carbethoxybenzene diazonium fluoborate precipitates; stirring is continued for 20 to 30 minutes and the solid is filtered. The crystals are washed successively with 300 cc. of cold water, 300 cc. of methanol, and 200 cc. of ether; the material is sucked as dry as possible between washings. The fluoborate is then dried over concentrated sulfuric acid (sp.gr. 1.84) in a vacuum desiccator. The yield of the dried fluoborate is 198 to 205 g. (75 to 78% of the theoretical amount); the decomposition point is 93° to 94°C.

The thermal decomposition can be carried out conveniently in a 2 liter distilling flask. A second distilling flask of 1 liter capacity is connected directly to the side arm of the first to serve as a receiver. The escaping gases are passed over water to absorb the boron trifluoride, and the other gases are led into a good hood. It is very important that the fluoborate is dry. If the solid is wet, the decomposition is very violent, tar is formed, and the yield is lowered.

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[107] *Organic Syntheses*, Wiley, New York, 1943, Coll. Vol. II, p. 295.

85 g. (0.32 mole) of *p*-carbethoxybenzene diazonium fluoborate are placed in the decomposition flask which is heated at its upper edge with a Bunsen flame. When the white fumes of boron trifluoride commence to appear, the flame is removed and the decomposition is permitted to proceed spontaneously. Heat is applied as necessary and finally the flask is strongly heated to decompose and melt the solid completely. The larger part of the ethyl *p*-fluorobenzoate, b.p. 105° to 106°C. at 25 mm., remains in the decomposition flask, but a small amount is collected in the receiver. The ester is refluxed for 1 hour on a steam bath with a solution of 56 g. (1 mole) of potassium hydroxide in 80 cc. of 95% ethyl alcohol and 120 cc. of water. The solution is filtered while still hot. The *p*-fluorobenzoic acid is precipitated by adding concentrated hydrochloric acid to the filtrate until the mixture is acid to Congo paper. After the mixture has cooled, the solid is filtered off and allowed to dry. The *p*-fluorobenzoic acid is dissolved in hot dilute potassium carbonate solution (40 g. in 400 cc.) and the solution is treated with Norite and filtered hot. Hydrochloric acid is added with stirring to precipitate the fluorobenzoic acid, which is then cooled, filtered, and dried. The yield is 38 to 40 g., corresponding to 84 to 89% of the theoretical amount; m.p. 186°C.

The present review summarizes the results of more recent investigations. It describes those methods which are of a general use and omits procedures which are applicable in special cases only.

For more recent information on this topic, see pages 593–595.

Catalysis of Organic Reactions by Boron Fluoride

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I. INTRODUCTION

During the last few years boron fluoride has been used as a catalyst for many reactions involving condensations, rearrangements, and polymerizations. It was shown to have an effect similar to that of gallium chloride, aluminum chloride, zinc chloride, ferric chloride, stannic chloride, antimony pentachloride, beryllium chloride, and other chlorides. Although boron fluoride is generally rather inferior in activity to aluminum chloride, which is probably the most used and most active of these catalytic agents, it is often quite advantageous to use boron fluoride, since reactions catalyzed by it usually proceed without the formation of undesirable byproducts. Such is not always the case with the other catalysts mentioned above.

That the reaction proceeds so smoothly probably depends on the fact that the small atomic volume and high electron affinity of boron fluoride allow it to form molecular compounds more stable than those of aluminum chloride, zinc chloride, ferric chloride, and the others. Many complex compounds of boron fluoride are distillable, and the solid ones crystallize from solvents of high dielectric constant, such as nitrobenzene, ether solutions of boron fluoride, and chlorobenzene.

In a molecular compound the molecule added to the catalyst, as has been shown by Meerwein,[1] is more or less strongly activated to such an extent that it can react with other molecules present in the mixture. Thus, in the presence of boron fluoride, ethers take on the properties of esters, esters assume those of acid anhydrides, and acid anhydrides become so reactive that they can react with aromatic compounds with the formation of ketones. In reactions catalyzed by aluminum chloride, components which lose hydrogen chloride during the course of the condensation react most easily. Boron fluoride, however, because of its great tendency to add to all oxygen-containing compounds, catalyzes most successfully those condensations in which water, an alcohol, or an organic acid is formed during the course of the reaction.

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[1] Meerwein, *Sitzber. Ges. Beförder ges. Naturw. Marburg,* **64,** 119 (1930); *Chem. Zentr.,* **1930, II,** 1962; *Chem. Abstracts,* **26,** 1871 (1932).

Not only is boron fluoride itself a powerful catalyst, as it promotes the reaction of a molecule combined with it, but also the great stability of the complex compounds makes them excellent catalysts for the condensations of a wide variety of substances. The molecular compounds of boron fluoride with water, organic acids, and alcohols have been particularly useful for this purpose. The complex formed from boron fluoride and phosphoric acid has also been employed for such reactions.[2] The work of Meerwein[3] has shown that complex formation increases the acidities of weak electrolytes in such a way that the complexes may resemble sulfuric acid or even perchloric acid[4] in their behavior; therefore the boron fluoride complexes of water, alcohols, and acids are often more useful than sulfuric or perchloric acids in promoting condensation reactions, since the latter often cause undesirable side reactions.

II. PREPARATION OF BORON FLUORIDE AND METHODS FOR ITS USE

Boron fluoride is quite easy to handle, as it is a gas (b.p. −101°C., m.p. −126°C.) which dissolves readily in most organic solvents. It can be bubbled into the reaction mixture directly, or it may be introduced as a solution of the gas in an organic solvent. Its preparation in the laboratory offers no difficulties, since it is not hydrolyzed by moisture to hydrofluoric acid. Instead, it reacts with water to form a monohydrate, $BF_3 \cdot H_2O$, and a dihydrate, $BF_3 \cdot 2H_2O$. The latter can be distilled *in vacuo* (b.p. 58.5° to 60°C. at 1 to 2 mm.) and can be stored in glass containers for any length of time by adding 1 to 2% of methanol to it.

The preparation of boron fluoride is carried out in an all-glass apparatus similar to that described by Pannwitz,[5] which was in operation for several years. The easiest method is that of Krause and Nitsche[6] in which a mixture of potassium borofluoride, boron trioxide, and concentrated sulfuric acid is heated. From 450 g. of potassium borofluoride, 75 g. of boron trioxide, and 1 liter of sulfuric acid a yield of 275 to 290 g. of boron fluoride is obtained. The product is expelled from the sulfuric acid by warming the mixture; small amounts can be measured out at any time by slowly raising the temperature from 150° to 240°C. In order to reduce to a minimum the amount of hydrofluoric acid formed during the preparation of the boron fluoride, it is essential to dissolve the finely powdered boron trioxide in the sulfuric acid and to add the borofluoride to the cool, stirred solution. A large reserve supply of boron fluoride can be acquired by dissolving the gas in anisole, from which it is easily regenerated by warming the solution gently. Boron fluoride is available commercially as a gas in steel cylinders. It can also be purchased in the form of its complex with diethyl ether.*

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[2] I. G. Farbenindustrie A.-G., German Patent 632,223.

[3] Meerwein, *Ann.*, **455**, 227 (1927).

[4] Compare also Klinkenberg and Ketelaar, *Rec. trav. chim.*, **54**, 959 (1935).

[5] Pannwitz, Thesis, Marburg, 1934, p. 19.

[6] Krause and Nitsche, *Ber.*, **54**, 2786 (1921). See also Schiff, *Ann.*, suppl., **5**, 172 (1867); Booth, in *Inorganic Syntheses*, McGraw-Hill, New York, 1939, Vol. I, p. 21; Booth and Willson, *J. Am. Chem. Soc.*, **57**, 2273 (1935). For the purification by distillation, see Booth and Bozarth, *Ind. Eng. Chem.*, **29**, 470 (1937). For the preparation from B_2O_3 and CaF_2, see Gasselin, *Ann. chim. phys.*, **3**, 6 (1894).

III. SYNTHESIS OF ESTERS, ALCOHOLS, NITRILES, AND SUBSTITUTED AMIDES

Since boron fluoride increases the acidities of organic acids and alcohols to a marked extent by complex formation, it is a good catalyst for esterifications. In the presence of 1 to 2% of boron fluoride, for example, acetic acid and ethanol afforded a 47 to 50% yield of ethyl acetate after having been refluxed for 1 hour.[7] Increasing the amount of catalyst or the period of refluxing gave no better yields. Whether the catalytic effect is due to the acetic acid-boron fluoride compound or to the complex with alcohol is a question which has not been answered. The yields of isopropyl esters obtained from monochloro-, dichloro-, and trichloroacetic acids, and from benzoic acid by refluxing for 3 hours, increased in the order in which the acids are named (Table I).

TABLE I

Comparison of Yields of Esters from Isopropyl Alcohol and Propylene[8]

Acid	Per cent yield of ester	
	With isopropyl alcohol	With propylene
Acetic	16.8	7
Chloroacetic	38.8	34.2
Dichloroacetic	48.6	39.5
Trichloroacetic	57.8	48
Benzoic	60.0	88

A similar increase in the yields of the esters was observed by Lichty[9] in the absence of a catalyst, but Sudborough and Lloyd[10] found that the order was reversed when hydrochloric acid was used as a catalyst in the esterification of these same acids with isopropyl alcohol, the yields of esters decreasing with increasing strengths of the acids.

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* Harshaw Chemical Co. and Eastman Kodak Co.

[7] Hinton and Nieuwland, *J. Am. Chem. Soc.*, 54, 2017 (1932).

[8] Dorris, Sowa, and Nieuwland, *J. Am. Chem. Soc.*, 56, 2689 (1934).

[9] Lichty, *Am. Chem. J.*, 18, 590 (1896).

[10] Sudborough and Lloyd, *J. Chem. Soc.*, 75, 467 (1899).

The esterification of substituted aromatic acids is usually more difficult than that of aliphatic acids, and the length of time for which reaction mixtures containing 1 mole of acid to 2 moles of alcohol have to be refluxed to obtain maximum yields varies from 15 minutes for benzoic acid to 5 hours for substituted benzoic acids.[11] The amount of ester formed is dependent in this case on the quantity of boron fluoride present, and as the amount of boron fluoride is increased the yield rises to a maximum, which is determined by the nature of the substituents. A further increase in the amount of boron fluoride is then without effect and in certain cases is even detrimental. The esterification of amino acids requires more than 1 mole of boron fluoride for each mole of acid, since the first mole of catalyst adds to the amino group with the formation of a stable coordinate covalent compound and thus has no catalytic effect. A maximum yield (53%) of methyl *p*-aminobenzoate requires the use of 3 moles of boron fluoride per mole of acid, but only 2 moles are necessary to prepare the best possible yield (85%) of methyl anthranilate.

Phenol and cresol esters of the resin acids have also been prepared by boron fluoride catalysis. The method is particularly advantageous, since the reaction can be carried out at low temperatures (room temperature when carbon tetrachloride is the solvent) and the products are clearer than those obtained by other methods, a factor which is quite important in their use for varnishes.[12]

Another method for the preparation of esters involves the treatment of acids with olefins in the presence of boron fluoride. The isopropyl esters in Table I were made by treating the corresponding acids with propylene in the presence of 3 g. of boron fluoride per mole of acid. The reactions were carried out at 60° to 70°C. for 16 hours under pressures up to 25 cm. above atmospheric pressure. The results obtained with benzoic acid are not directly comparable to those from the aliphatic acids, since the conditions were modified somewhat in that case. These reactions would undoubtedly be quantitative, if the reaction time were increased. The increasing speed of esterification indicated in Table I is not due entirely to the increasing acidity of the acids, but it is probably connected also with the greater solubility of propylene in the chlorinated acids and their esters. The solubilities of propylene per mole of acid or ester at a pressure of 25 cm. in excess of atmospheric pressure are given in Table II.

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[11] Sowa and Nieuwland, *J. Am. Chem. Soc.*, **58**, 271 (1936).

[12] I. G. Farbenindustrie A.-G., German Patents 582,846, 582,847 and 605,688; British Patents 399,211 and 400,627.

TABLE II

Solubilities of Propylene in Chlorinated Acetic Acids and Their Esters

Substituent	0 Cl	1 Cl	2 Cl	3 Cl
Acid	0.96	1.71	2.41	2.69
Ester	1.40	1.90	2.99	3.76

Other olefins, such as butylene or β-amylene, and other acids including the dibasic acids behave similarly. In the case of the higher alkenes, the reaction temperature must be maintained below 100°C. to prevent excessive polymerization of the olefin. The esterification reaction follows Markovnikov's rule, the ester group always appearing on the carbon atom having the greatest number of alkyl groups. As a result, olefins always produce secondary or tertiary alkyl esters. On the other hand, when cyclopropane is used, *n*-propyl esters are formed.[13]

The dependence of ester formation and polymerization on the quantity of boron fluoride was studied quantitatively by Wunderly and Sowa[14] for the reaction between cyclohexene and excess acetic acid. The temperature was controlled to 80°C. and the reaction time was varied from 50 to 220 hours. They found that a maximum yield of cyclohexyl acetate (65%) was obtained when 6 to 10% of boron fluoride was present in the reaction mixture, but as the quantity of boron fluoride was increased above 10% the yield of ester dropped and the amount of polymer produced increased very rapidly.

A reaction of interest in connection with the esterification of acids by olefins is that of the polymerization of undecylenic acid. When the acid was treated with boron fluoride, much heat was evolved and an oily polymer was obtained. The product contained some carboxyl groups, but analysis showed that it was primarily a polyester resulting from the esterification of the carboxyl groups by the olefin portion of the molecule. Some olefin polymerization appeared to have taken place, but it was not so extensive as the esterification reaction.[15]

The treatment of the boron fluoride-acetamide complex by alcohols or phenols also gives esters of acetic acid.[16]

$$CH_3CONH_2 \cdot BF_3 + ROH \longrightarrow CH_3COOR + NH_3 \cdot BF_3$$

The driving force in this reaction is the pronounced tendency for boron fluoride to form a coordination complex with ammonia. Evidence for this is the fact that the quantity of boron fluoride present in the reaction mixture has a direct effect on the yield of the ester.

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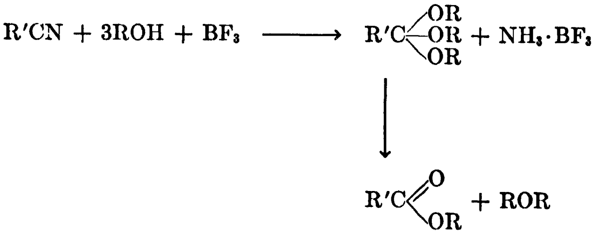
[13] Dorris and Sowa, *J. Am. Chem. Soc.*, 60, 358 (1938).
[14] Wunderly and Sowa, *J. Am. Chem. Soc.*, 59, 1010 (1937).
[15] Cann and Amstutz, *J. Am. Chem. Soc.*, 66, 839 (1944).
[16] Sowa and Nieuwland, *J. Am. Chem. Soc.*, 55, 5052 (1933).

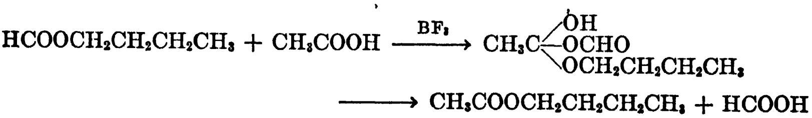
Molar quantities of boron fluoride promote the reaction of alcohols with nitriles,[17] which takes the course shown in Equation 1.



$$R'CN + 3ROH + BF_3 \longrightarrow R'C(OR)_3 + NH_3 \cdot BF_3 \longrightarrow R'C\begin{matrix}\diagup O \\ \diagdown OR\end{matrix} + ROR \qquad (1)$$

When acetonitrile and *n*-propyl alcohol were refluxed for 1 hour in the presence of boron fluoride, *n*-propyl acetate (28%) and di-*n*-propyl ether (27%) were formed. With *n*-butyl alcohol the product consisted of 48% of *n*-butyl acetate and 28% of di-*n*-butyl ether. The reaction is not confined to aliphatic nitriles, as benzonitrile reacted with *n*-propyl alcohol and produced *n*-propyl benzoate (30%) and di-*n*-propyl ether (26%). The isolation of ether (0.28 mole) and ethyl formate (0.28 mole) as their complexes with boron fluoride from the reaction mixture obtained by saturating 0.33 mole ethyl orthoformate with 0.56 mole boron fluoride is a convincing proof that the ortho ester is the intermediate in this type of reaction.

The esters of formic, propionic, benzoic, and salicylic acids have been transformed into the corresponding acetates by heating them at 100°C. for as short a time as 1 hour with a solution of boron fluoride in acetic acid.[18] *n*-Butyl formate gave *n*-butyl acetate along with about 4% of a secondary or tertiary butyl ester when treated with this reagent. The mechanism shown in Reaction 2 has been accepted for the acetolysis reaction. The



$$HCOOCH_2CH_2CH_2CH_3 + CH_3COOH \xrightarrow{BF_3} CH_3C\begin{matrix}\diagup OH \\ -OCHO \\ \diagdown OCH_2CH_2CH_2CH_3\end{matrix} \qquad (2)$$
$$\longrightarrow CH_3COOCH_2CH_2CH_2CH_3 + HCOOH$$

formation of secondary and tertiary butyl acetates is probably due to the cleavage of part of the ester into formic acid and the olefin and the subsequent addition of the olefin to acetic acid. Sulfuric acid and zinc chloride have been found to be much less active than boron fluoride for catalyzing this reaction.

Olefins add water in much the same way that they add acids. Propylene reacts with boron fluoride dihydrate and gives isopropyl alcohol and diisopropyl ether.[19] The reaction is limited to secondary olefins and does not proceed very well, since a polymer of propylene is always formed as a by-product. In the case of tertiary olefins only the polymer is obtained.[20] On the other hand tertiary olefins might be expected to react with alcohols in the presence of boron fluoride at temperatures below 100 °C. Such a reaction does take place between methanol and trimethylethylene, and it produces methyl *tert*-amyl ether.[21] Dihydric alcohols such as ethylene glycol also react with olefins in the presence of boron fluoride and copper, nickel, or silver catalysts with the formation of mono- or dialkyl ethers of ethylene glycol.[22]

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[17] McKenna and Sowa, *J. Am. Chem. Soc.*, 60, 124 (1938).
[18] Sowa, *J. Am. Chem. Soc.*, 60, 654 (1938).

Since esters are readily obtained from the reaction between boron fluoride-amide complexes and alcohols, it would be expected that an acid anhydride would result from the analogous reaction between a boron fluoride-amide complex and a carboxylic acid. Such a reaction does not take place, but instead nitriles are formed nearly quantitatively.[23] The reaction proceeds as in Equation 3. Instead of entering into the reaction the

$$CH_3CONH_2\cdot BF_3 + CH_3CONH_2 \xrightarrow{CH_3COOH} CH_3CN + CH_3COOH + NH_3\cdot BF_3 \quad (3)$$

acid (acetic, propionic, or hydrochloric acid) present in the mixture merely serves to initiate the reaction. In one-half hour the reaction is complete in a refluxing mixture containing $^1/_{15}$ mole of acid. The nitrile corresponding to the amide used is always obtained. Without the addition of an acid only a 15% yield of acetonitrile is formed.

The boron fluoride complexes of the acid amides when refluxed with primary and secondary aliphatic and with aromatic amines (Eq. 4) produce the corresponding substituted amides within 30 minutes.[23] The yields of

$$CH_3CONH_2\cdot BF_3 + HN\begin{matrix}R\\R\end{matrix} \longrightarrow CH_3CON\begin{matrix}R\\R\end{matrix} + NH_3\cdot BF_3 \quad (4)$$

substituted amides obtained in the reaction between the boron fluoride-

TABLE III

Reaction between Amines and Acetamides

Amine	Product	Yield, %
n-Butylamine	*N*-Butylacetamide	37
Di-*n*-butylamine	*N*,*N*-Dibutylacetamide	27
Aniline	*N*-Phenylacetamide	33
N-Methylaniline	*N*-Methyl-*N*-phenylacetamide	54

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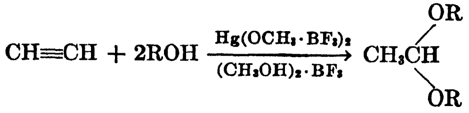
[19] Meerwein and Burneleit, *J. prakt. Chem.*, 141, 139 (1934).
[20] Kästner, unpublished work.
[21] Standard Oil Development Co., U. S. Patent 2,197,023.
[22] I. G. Farbenindustrie A.-G., U. S. Patent 2,198,046.
[23] Sowa and Nieuwland, *J. Am. Chem. Soc.*, 59, 1202 (1937).

acetamide coordination complex and a number of amines are given in Table III. Propionamide and benzamide react in a similar way to give *N*-phenyl propionamide (97%) and benzanilide (37%), respectively.

IV. REACTIONS OF UNSATURATED ALIPHATIC COMPOUNDS

1. Synthesis of Acetals by Alcoholysis of Acetylenes

Since the acidity of a weak electrolyte is increased markedly by complex formation (see Section III), it is not surprising that the coordination complexes of boron fluoride and alcohols are strong acids which resemble sulfuric acid. Because of the fact that mercuric oxide is soluble in alcoholic solutions of boron fluoride, such a solution can be used instead of the usual catalyst, a solution of mercuric sulfate in sulfuric acid, for the condensation of acetylenes with alcohols, hydroxy acids, and carboxylic acids. An example of this type of reaction is the condensation of acetylene and methanol with the formation of the dimethyl acetal of acetaldehyde.[24]



$$CH{\equiv}CH + 2ROH \xrightarrow[(CH_3OH)_2\cdot BF_3]{Hg(OCH_3\cdot BF_3)_2} CH_3CH(OR)_2 \qquad (5)$$

O'Leary and Wenzke have isolated the mercury salt of the boron fluoride-methanol complex, $Hg(OCH_3 \cdot BF_3)_2$, which must be the catalyst in the reaction in which the acetal is formed.[25] This reaction is applicable to the condensations of acetylene with almost all the monohydric alcohols.[26] Since halogen ions interfere with the condensation, it is assumed that they cause the formation of mercuric chloride, which removes the catalyst in the form of a salt which has no catalytic effect.

The preparation of acetaldehyde diisoamyl acetal was carried out by dissolving 29.5 g. of acetylene in 200 g. of isoamyl alcohol which contained 10 g. of a 63% solution of boron fluoride in methanol and 1 g. of mercuric oxide. At the end of the reaction a little water and a little sodium carbonate were added to the mixture. The organic products were then extracted with ether, and the ether extract was dried over potassium carbonate and fractionated. In the preparation of acetals very sensitive to acids (especially the acetals of ketones) it was essential that the reaction mixture be neutralized with anhydrous sodium carbonate in order to prevent hydrolysis of the product.

By similar procedures acetylene has been condensed with the primary alcohols up to amyl alcohol, the tertiary alcohols up to nonyl alcohol, and various aromatic alcohols. The acetals formed in these cases acted as solvents and accelerated the reactions. Tertiary alcohols gave acetals with increasing ease as their carbon content increased, and no olefins were formed in side reactions. The yields of acetals from the various alcohols varied from 30 to 54%.

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[24] Bowlus and Nieuwland, *J. Am. Chem. Soc.*, 53, 3835 (1931); E. I. du Pont de Nemours and Co., U. S. Patent 2,140,713.

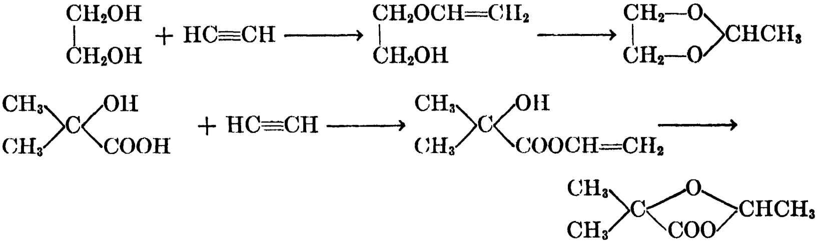
[25] O'Leary and Wenzke, *J. Am. Chem. Soc.*, 55, 2117 (1933).

[26] Hinton and Nieuwland, *J. Am. Chem. Soc.*, 52, 2892 (1930).

Borneol and terpineol do not form acetals, and although cyclohexanol reacts very slowly, the product is a tar. Furfuryl alcohol undergoes decomposition during the reaction, but tetrahydrofurfuryl alcohol reacts smoothly. Amino alcohols cannot be used in the condensation, since boron fluoride forms a coordination complex with the amine group and becomes unavailable for catalysis. Oximes do not condense with acetylene in the presence of boron fluoride and mercury catalysts.

The method of preparing acetals with boron fluoride as the catalyst is often more advantageous than that with sulfuric acid, since usually fewer by-products are formed and the utilization of mercury is more efficient. Many acetals such as those of benzyl alcohol, which cannot be prepared by any other method, can be made by this procedure.

Acetylene reacts in this way not only with monohydric alcohols but also with polyhydroxy compounds and α-hydroxy acids and their derivatives.[27] The reaction proceeds by two steps as illustrated by Equations 6.



(6)

Halogen substituents and ester and ether groups are unaffected during the course of the condensation. The following polyalcohols and hydroxy acids have been used to prepare the corresponding ethylidene compounds by this method (the yields are given in parentheses): ethylene glycol (62%), trimethylene glycol (45%), pinacol, methyl ethyl pinacol, ethylene glycol monomethyl ether (44%), ethylene glycol monoethyl ether (74%), ethylene glycol monobutyl ether (52%), ethylene glycol diethyl ether, diethylene glycol monoethyl ether, glycerol monomethyl ether (60%), glycerol monoethyl ether, glycerol α-phenyl ether (68%), ethylene chlorohydrin (71%), trimethylene chlorohydrin (38%), glycerol chlorohydrin (72%), glyceryl monoacetate (49%), lactic acid (61%), α-hydroxyisobutyric acid (71%), dimethyl *d*-tartrate (81%), diethyl *d*-tartrate (74%), malic acid β-methyl ester (26%), malic acid β-ethyl ester (30%), dimethyl citrate (31%), mandelic acid (64%), benzilic acid (66%).

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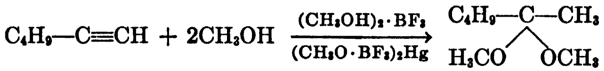
[27] Nieuwland, Vogt, and Foohey, *J. Am. Chem. Soc.*, **52**, 1018 (1930).

Glycerol reacts with acetylene with the formation of 78% of the 1,2-acetal and 22% of the 1,3-acetal, both of which can react with more acetylene, thus producing diglycerol triethylidene ether (41.7%). Similarly, pentaerythritol and mannitol react with more than 1 mole of acetylene. From pentaerythritol is obtained pentaerythritol diethylidene ether (90%), and from mannitol, mannitol triethylidene ether (47%). Such well defined acetals are not always obtained in reactions of hydroxy compounds with acetylene, as some products, which should be acetals, offer special problems with regard to their isolation. One hydroxy compound which for some peculiar reason does not react with acetylene is glycolic acid.

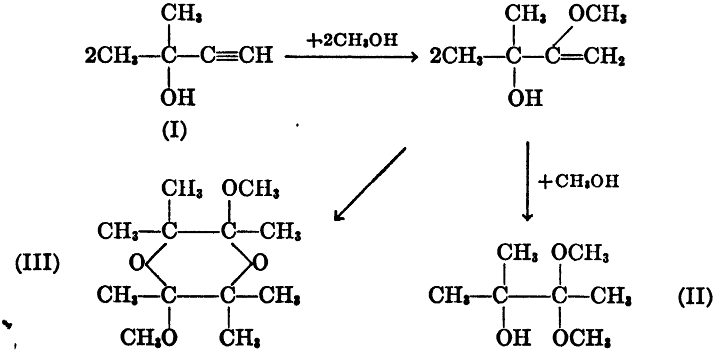
The alkylated acetylenes form ketals with methanol in the presence of boron fluoride dialcoholate and its mercury salt in the same way that unsubstituted acetylenes react[28,29] (Eq. 7). Methyl-, ethyl-, and *n*-amylacetylenes react with methanol in this way.



$$C_4H_9{-}C{\equiv}CH + 2CH_3OH \xrightarrow[(CH_3O\cdot BF_3)_2Hg]{(CH_3OH)_2\cdot BF_3} C_4H_9{-}C(OCH_3)_2{-}CH_3 \qquad (7)$$

The preparation of *n*-butyl methyl ketone dimethyl acetal in 70% yield was effected by stirring *n*-butylacetylene and methanol for 2 hours at 30° to 40°C. in the presence of the catalyst. The catalyst was added in the form of the ether complex of boron fluoride and mercuric oxide.

Dimethylethynylcarbinol (I) reacts with methanol[30] and produces 2-methyl-3,3-dimethoxy-2-butanol (II) in 80% yield. A trace (4.4%) of 2,5-dimethoxy-2,3,3,5,6,6-hexamethyl-1,4-dioxane (III) is formed as a by-product. Reactions with methanolic solutions of methylethyl- or



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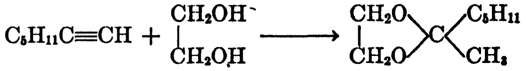
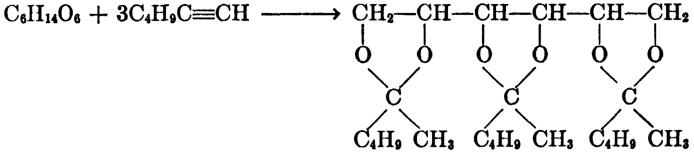
[28] Hennion, Killian, Vaughan, and Nieuwland, *J. Am. Chem. Soc.*, 56, 1130 (1934).
[29] Killian, Hennion, and Nieuwland, *J. Am. Chem. Soc.*, 56, 1384 (1934).
[30] Fronning and Hennion, *J. Am. Chem. Soc.*, 62, 653 (1940).

diethylethynylcarbinols in the presence of boron fluoride lead to the production of ketals corresponding to II. According to Nazarov and Nagibina, these ketals cyclized only with difficulty in contrast to the behavior of II, but nevertheless some of the dioxane derivative from the cyclization of the product from methylethylethynylcarbinol was isolated from the reaction mixture.[31]

Other monohydric alcohols do not form ketals in reactions with acetylene. Ethanol reacts very vigorously with amylacetylene, but only polymeric products can be isolated. On the other hand, polyhydric alcohols and α-hydroxy acids condense smoothly with alkylacetylenes. An example of the use of such a compound is the reaction between amylacetylene and ethylene glycol, which produces the corresponding cyclic acetal of amyl methyl ketone.[28]



Butylacetylene reacts in the same way with ethylene glycol, glycerol monochlorohydrin, dimethyl tartrate, mannitol, α-hydroxybutyric acid, and mandelic acid.[32] Mannitol, which has six hydroxyl groups, reacts with 3 moles of butylacetylene.



That the reaction producing ketals is not limited to monoalkylacetylenes was shown by the condensation of amylmethylacetylene with methanol by the method described above. The product was isolated in a yield of 55%.[33] In this case it was possible to demonstrate that the intermediate in the reaction was not mercury acetylide, as O'Leary and Wenzke[25] had assumed in suggesting their reaction mechanism mentioned previously. Instead, an addition product in which the mercury salt of the boron fluoride alcoholate had added to the triple bond effected the condensation.

Methanol has also been added to the disubstituted acetylene (IV)[30] but the ketal (V) resulting from the initial condensation undergoes ring closure with the elimination of water. The water then hydrolyzes the acetal linkages, and the product isolated from the reaction mixture is 2,2,5,5-tetramethyltetrahydro-3-furanone (VII) (75% yield). The same sub-

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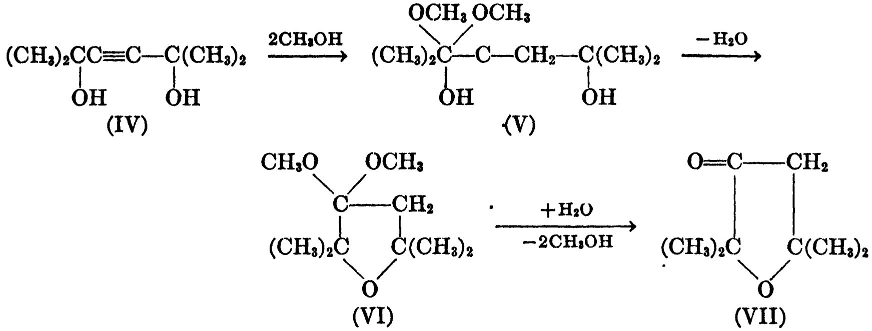
[31] Nazarov and Nagibina, *Bull. acad. sci. U. R. S. S., Cl. sci. chim.*, **1941**, 303; *Chem. Abstracts*, **37**, 5368 (1943).

[32] Killian, Hennion, and Nieuwland, *J. Am. Chem. Soc.*, **58**, 1658 (1936).

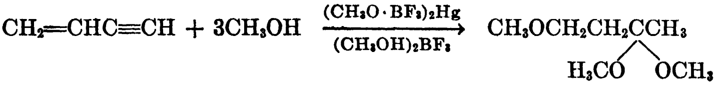
[33] Hennion and Nieuwland, *J. Am. Chem. Soc.*, **57**, 2006 (1935).



stance is obtained if acetic acid is used in place of methanol for the condensation.

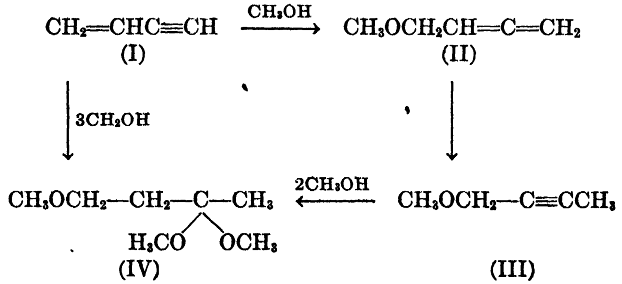
2. Reactions of Vinylacetylenes

Vinylacetylene is especially interesting, since the conjugation of the double with the triple bond makes the ethylenic linkage capable of undergoing the addition of methanol also. This compound therefore reacts with 3 moles of methanol in the presence of mercuric oxide and boron fluoride and forms 2,2,4-trimethoxybutane.[34] The condensation proceeds more smoothly if small quantities of trichloroacetic acid are added to the mixture.



$$CH_2{=}CHC{\equiv}CH + 3CH_3OH \xrightarrow[(CH_3OH)_2BF_3]{(CH_3O\cdot BF_3)_2Hg} CH_3OCH_2CH_2C(OCH_3)_2CH_3$$

The reaction was carried out by adding 480 g. (15 moles) of methanol to a mixture of 15 g. of mercuric oxide, 4.5 cc. of boron fluoride etherate, 2 g. of trichloroacetic acid, and 10 cc. of methanol. Then 312 g. (6 moles) of vinylacetylene were passed into the mixture while the temperature gradually increased from 15° to 50°C. There were obtained 487 g. of 2,2,4-trimethoxybutane. Proof that the product was an acetal was obtained by hydrolysis of the compound to 4-methoxy-2-butanone.



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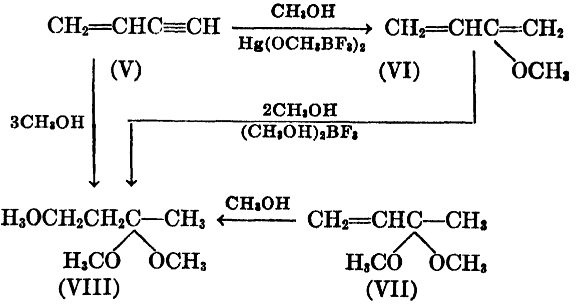
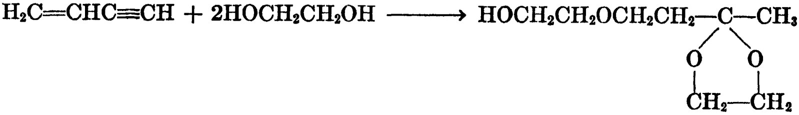
[34] Killian, Hennion, and Nieuwland, *J. Am. Chem. Soc.*, **56**, 1786 (1934).

Since 4-methoxy-2-butyne (III) added methanol easily in the presence of boron fluoride alcoholate and produced 2,2,4-trimethoxybutane (IV),[35] the investigators believed that the addition of methanol to vinylacetylene took the course shown in formulas I to IV.

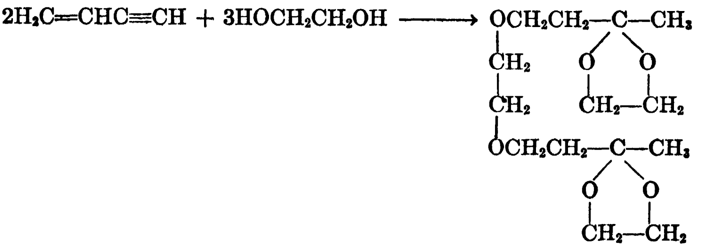
It is probable, however, that instead of a 1,4 addition of methanol to vinylacetylene; the first step is an addition of methanol to the triple bond.[36] Further evidence for this has been obtained by Norris, Verbanc, and Hennion,[37] who found that methanol adds very smoothly to both 2-methoxy-1,3-butadiene (VI) and 2,2-dimethoxy-3-butene (VII) in acid media with the production of 2,2,4-trimethoxybutane (VIII).



Vinylacetylene reacts with ethylene glycol under the same conditions which favor the addition of methanol. The two products which have been isolated are formed as shown in the Equations 8 and 9.



(8)



(9)

Not only vinylacetylene but also the alkyl-substituted vinylacetylenes[34] add 3 moles of methanol quite easily in the presence of this catalyst.

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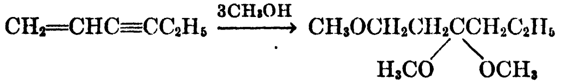
[35] Killian, Hennion, and Nieuwland, *J. Am. Chem. Soc.*, **58**, 892 (1936).

[36] Rotenberg and Favorskaya, *J. Gen. Chem. U. S. S. R.*, **6**, 185 (1936); *Chem. Abstracts*, **30**, 4808 (1936).

[37] Norris, Verbanc, and Hennion, *J. Am. Chem. Soc.*, **60**, 1159 (1938).

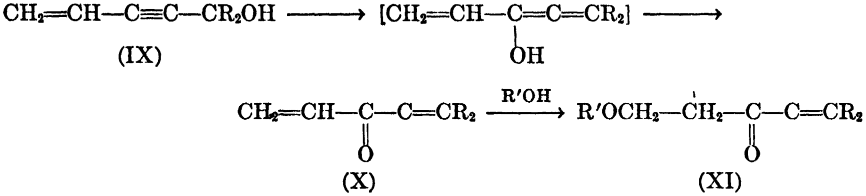
From the reaction (Eq. 10) between vinylethylacetylene and methanol is obtained 1,3,3-trimethoxyhexane.



(10)

The addition of methanol to divinylacetylene could not be established with certainty even though various changes were made in the conditions of the reaction. Other reactions involving the polymerization of divinylacetylene and the reduction of the mercury catalyst took precedence over the addition reaction.

Experiments with tertiary vinylethynylcarbinols have shown that a uniform mechanism is operative in the addition reactions of alcohols to them in the presence of boron fluoride etherate and mercuric oxide. The tertiary carbinol (IX) is first isomerized to a divinyl ketone (X) which adds 1 mole of alcohol with the production of the ether (XI). The reaction takes place in 3 or 4 hours at temperatures of 25° to 30°C. Methyl, ethyl, and *n*-propyl alcohols give colorless mobile oils in yields of 65 to 77%, which do not polymerize even at 100° and in the presence of benzoyl peroxide.[38]



$$\underset{\text{(IX)}}{\mathrm{CH_2{=}CH{-}C{\equiv}C{-}CR_2OH}} \longrightarrow [\mathrm{CH_2{=}CH{-}\underset{\substack{|\\ OH}}{C}{=}C{=}CR_2}] \longrightarrow$$

$$\underset{\text{(X)}}{\mathrm{CH_2{=}CH{-}\underset{\substack{\|\\ O}}{C}{-}C{=}CR_2}} \xrightarrow{\mathrm{R'OH}} \underset{\text{(XI)}}{\mathrm{R'OCH_2{-}CH_2{-}\underset{\substack{\|\\ O}}{C}{-}C{=}CR_2}}$$

Secondary vinylethynylcarbinols are isomerized in a similar way by the action of methanol solutions of mercuric salts and boron fluoride. The β-alkyl divinyl ketones which are formed add 2 moles of methanol under the experimental conditions employed, with the production of compounds of the type, $\mathrm{R\underset{\substack{|\\ OCH_3}}{C}HCH_2COCH_2CH_2OCH_3}$. The corresponding divinyl ketones can be prepared by the removal of methanol by *p*-toluenesulfonic acid.[39]

In compounds in which the double bond is not conjugated with the triple bond only the acetylenic bond is involved in reactions with methanol. Thus allylalkylacetylenes react with methanol in the presence of the mercuric oxide-boron fluoride catalyst to produce 5,5-dimethoxy-1-alkenes, as illustrated by Equation 11, in which R = alkyl (C_4H_9—, C_5H_{11}—) or phenyl.

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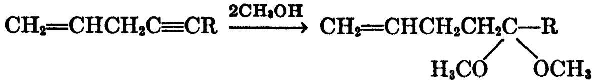
[38] Nazarov and Romanov, *Bull. acad. sci. U. R. S. S., Cl. sci. chim.*, **1940**, 453; *Chem. Abstracts*, **35**, 3593 (1941).

[39] Nazarov and Okolskaya, *Bull. acad. sci. U. R. S. S., Cl. sci. chim.*, **1941**, 314; *Chem. Abstracts*, **37**, 5369 (1943).



$$CH_2{=}CHCH_2C{\equiv}CR \xrightarrow{2CH_3OH} CH_2{=}CHCH_2CH_2\underset{H_3CO\quad OCH_3}{C}{-}R \qquad (11)$$

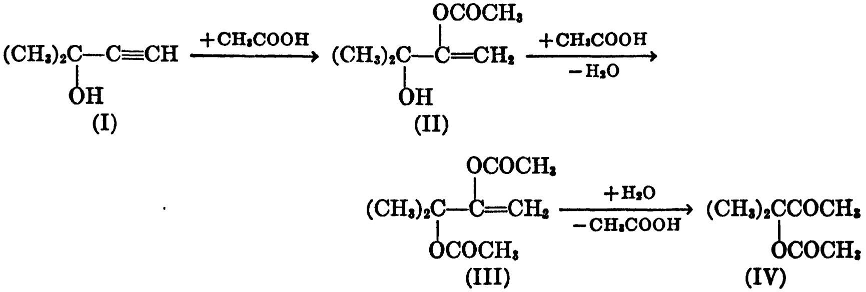
On the other hand, when a double bond is activated by conjugation with a carbonyl group, methanol adds to it in the presence of the catalyst. In this way β-methoxyethyl methyl ketone was obtained in a 61% yield from vinyl methyl ketone.

$$CH_2{=}CHCOCH_3 \xrightarrow[HgO,\,BF_3]{CH_3OH} CH_3OCH_2CH_2COCH_3 \qquad (12)$$

3. Preparation of Vinyl (Enol) Esters

The reaction of acetylene and its alkyl derivatives with organic acids follows a course similar to that with methanol. In these cases vinyl esters (enol esters) are formed. When acetylene is passed for 6 to 8 hours into warm (20° to 25°C.) acetic acid, containing about 1% of mercuric oxide and 1% of boron fluoride-diacetic acid, there is isolated an 80% yield of vinyl acetate.[40] Similarly vinyl butyrate is formed from butyric acid. In contrast to other methods which have been used for the production of vinyl esters, this reaction proceeds at much lower temperatures and with a minimum of side reactions. Hydrolysis of the enol esters produces methyl ketones, a reaction which has been of some importance.

This reaction is also applicable to the alkylacetylenes, from which are obtained substituted vinyl esters.[28,41] Examples of this reaction are the production of 60 g. of 2-chloroacetoxy-1-hexene from the reaction between 47.3 g. of chloroacetic acid and 55 g. of butylacetylene at 0°C., and the isolation of 45 g. of the enol benzoate of butyl methyl ketone by warming a mixture of 61 g. of benzoic acid and 82 g. of butylacetylene. The addition of acetic acid to compound I has been accomplished with the formation of II,[30] but simultaneously with this reaction esterification of the hydroxyl



$$\underset{\text{(I)}}{(CH_3)_2\underset{OH}{C}{-}C{\equiv}CH} \xrightarrow{+CH_3COOH} \underset{\text{(II)}}{(CH_3)_2\underset{OH}{C}{-}\overset{OCOCH_3}{C}{=}CH_2} \xrightarrow[-H_2O]{+CH_3COOH}$$

$$\underset{\text{(III)}}{(CH_3)_2\underset{OCOCH_3}{C}{-}\overset{OCOCH_3}{C}{=}CH_2} \xrightarrow[-CH_3COOH]{+H_2O} \underset{\text{(IV)}}{(CH_3)_2\underset{OCOCH_3}{C}COCH_3}$$

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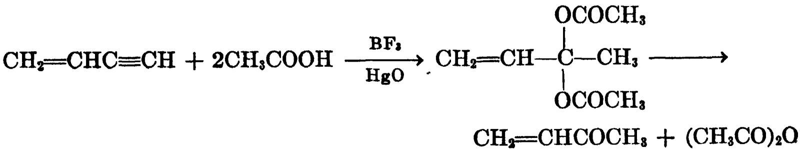
[40] Zal'kind, Aizikovich, Vovsi, and Ivanov, *Trans. Leningrad Chem.-Tech. Inst.*, II (1935).

[41] Hennion and Nieuwland, *J. Am. Chem. Soc.*, 56, 1802 (1934).

group took place. The enol acetate was hydrolyzed by the water produced in the latter reaction, and the rearrangement of the enol thus formed produced 3-acetoxy-3-methyl-2-butanone (IV).

The hydration of the 17-ethynyl derivatives of certain steroids and sex hormones by Nieuwland's method and the subsequent saponification of the enol acetate so obtained with the production of the corresponding methyl ketones have been reported by Ruzicka and co-workers.[42] Hydroxyl groups in the molecules were acetylated during the process, since a mixture of boron fluoride, acetic anhydride, and acetic acid is a very strong acetylating agent even in the absence of mercuric oxide. This method of acetylating hydroxy groups in the steroids has been found to be somewhat superior to the acetic anhydride-pyridine method, and it has been used for acetylating successfully compounds which resisted esterification by the older method.[43]

A second mode of reaction of monosubstituted acetylenes and aliphatic carboxylic acids has been observed. According to a process assigned to the I. G. Farbenindustrie,[44] vinyl methyl ketone and acetic anhydride are obtained in an 80% yield from the reaction between vinylacetylene and acetic acid at 25° to 30°C. in the presence of a boron fluoride-mercuric oxide catalyst. According to Nieuwland the reaction probably involves the mechanism shown in Equation 13.



$$CH_2{=}CHC{\equiv}CH + 2CH_3COOH \xrightarrow[HgO]{BF_3} CH_2{=}CH{-}\underset{\displaystyle OCOCH_3}{\overset{\displaystyle OCOCH_3}{\overset{|}{\underset{|}{C}}}}{-}CH_3 \longrightarrow CH_2{=}CHCOCH_3 + (CH_3CO)_2O \qquad (13)$$

4. Polymerization, Isomerization, and Cyclization of Olefins

The polymerization of olefins has been employed most extensively during the last few years for the production of fuels, lubricating oils, synthetic polymers, and intermediates for use in other condensation reactions. Boron fluoride and its coordinate complexes have been useful catalysts for these reactions (in addition to aluminum chloride, phosphoric acid, sulfuric acid, and others) and the patent literature contains numerous examples of reactions catalyzed by them. This work has shown that in general the tendency toward polymerization increases in olefins with increasing substitution on one of the ethylenic carbon atoms. Thus, isobutylene is more reactive than propylene and propylene polymerizes more easily than does ethylene.

[42] L. Ruzicka and Meldahl, *Helv. Chim. Acta*, 21, 1760 (1939); L. Ruzicka, Gätzi, and Reichstein, *ibid.*, 22, 626 (1939); L. Ruzicka, Goldberg, and Hunziker, *ibid.*, 22, 707 (1939).

[43] Shoppee and Prins, *Helv. Chim. Acta*, 26, 201 (1943).

[44] I. G. Farbenindustrie A.-G., German Patent 590,237.

The first observations on the polymerization of olefins with boron fluoride as the catalytic agent were those of Saint Claire Deville,[45] who transformed pinene into a dimer called *colophene*. Later it was discovered by Butlerow and Goriainow,[46] Landolph,[47] and Gasselin[48] that other olefins such as propylene and amylene could be polymerized to hydrocarbons of higher molecular weight in the presence of boron fluoride. A patent owned by Bayer,[49] describes a method for the polymerization of butadienes by boron halides. A similar process produces mixed polymers from butadiene hydrocarbons and styrene.[50] The condensation of isocyclic olefins has also been accomplished by the use of boron fluoride. They form elastic materials which can be vulcanized just like rubber.[51] Furthermore, Hofmann and Stegemann[52] have shown that cumarone oil can be polymerized to cumarone resin, and by a similar process,[53] patented by the I. G. Farbenindustrie, products are obtained by the polymerization of natural resins (colophony-abietic acid, dammar copal) in solution in organic solvents in the presence of boron fluoride. These polymers differ from the starting materials by having markedly lower iodine numbers, higher molecular weights, and (usually) higher softening points. They also show none of the color reactions characteristic of the natural resins.

The polymerization of all the gaseous olefins, including ethylene, was finally realized by Hofmann and Otto[54] by working under pressure. The products are oils, the viscosities of which depend on the temperatures and pressures involved in the condensation. Rectification of a typical polymer obtained from ethylene gave the following fractions: 0.5% b.p. up to 100 °C. at 15 mm., 8% b.p. 100° to 150 °C. at 15 mm., 18% b.p. up to 150 °C. at 3 mm., and 40% b.p. 150° to 200 °C. at 3 mm. The best products and yields were obtained when the ratio of the weight of boron fluoride to that of ethylene was 1:10, and when the reaction was conducted at room temperature.[55] While a mixture of 100 g. of ethylene and 10 g. of boron fluoride under a pressure of 130 atmospheres afforded 85 to 96 g. of polymer in 8 hours at room temperature, the same mixture gave only 10 g. at 0 °C. The yields at other temperatures were as follows: 100 °C., 37 g.; 200 °C., 60 g.; 300 °C., 73 g.

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[45] Saint Claire Deville, *Ann. chim.*, **75**, 66 (1839).

[46] Butlerow and Goriainow, *Ann.*, **169**, 146 (1873); *Ber.*, **6**, 561 (1873).

[47] Landolph, *Ber.*, **12**, 1578 (1879).

[48] Gasselin, *Ann. chim.*, **3**, 5 (1894).

[49] Bayer and Co., German Patent 264,925.

[50] I. G. Farbenindustrie A.-G., French Patent 848,411.

[51] I. G. Farbenindustrie A.-G., German Patent 695,135.

[52] F. Hofmann and Stegemann, German Patent 492,345.

[53] I. G. Farbenindustrie A.-G., German Patent 564,897.

[54] F. Hofmann and Otto, German Patents 505,265 and 512,959; French Patent 632,768; British Patent 293,487.

[55] Otto, *Brennstoff-Chem.*, **8**, 321 (1927); *cf.* Nash, Stanley, and Bowen, *Petroleum Times*, **24**, 799 (1930).

In the preparation of lubricating oils the olefins obtained by the cracking and dehydrogenation of paraffin hydrocarbons have been polymerized by boron fluoride catalysts.[56] Similar polymers possessing the properties of lubricating oils have been produced by a process assigned to the I. G. Farbenindustrie, in which derivatives of hydrocarbons (such as halogen compounds, ethers, or esters) and unsaturated hydrocarbons of the ethylene or acetylene series are treated with boron fluoride or aluminum chloride.[57]

The polymerization of olefins by the use of boron fluoride has been proposed as a method for the purification of hydrocarbon oils such as crude benzene.[58] The olefin constituents of the hydrocarbon mixtures were polymerized by the addition of about 1% of boron fluoride. After the catalyst had been removed by washing the reaction mixture with water, the polymer was separated by distillation.

The rate at which the olefins polymerize is increased markedly if a little hydrofluoric acid or water is present in addition to the boron fluoride.[59] For example, 100 g. of dry propylene in the presence of 3 g. of boron fluoride at room temperature gave 30 g. of polymer in 15 hours, but wet propylene under the same conditions yielded 70 to 75 g. The addition of 1g. of hydrogen fluoride to the reaction mixture, however, caused the quantitative polymerization of propylene in 30 minutes. The same effects were observed in the polymerization reactions of ethylene, butylene, and cyclohexene.

Another means of increasing the rate of polymerization is to add finely divided nickel to the reaction mixture containing boron fluoride.[60] Ethylene is polymerized quantitatively in the presence of nickel under conditions which would otherwise lead to the formation of only 20% of the polymer. The oils obtained are different inasmuch as those produced in the presence of nickel are less viscous than those formed by boron fluoride alone. The dimerization of ethylene to 2-butene can be effected by passing a mixture of liquid ethylene and boron fluoride over nickel under a pressure of 50 atmospheres. The temperature of the reactants is kept at 8° to 10°C. and the time during which they are in contact with the nickel is kept at a minimum to prevent the reaction from proceeding further.[61]

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[56] I. G. Farbenindustrie A.-G., German Patent 546,082; British Patent 354,441.

[57] I. G. Farbenindustrie A.-G., French Patent 695,125.

[58] F. Hofmann, Dunkel, and Heyn, German Patent 550,429.

[59] F. Hofmann, Otto, and Stegemann, German Patent 507,919; British Patent 313,067; U. S. Patent 1,885,060; E. I. du Pont de Nemours and Co., U. S. Patent 2,183,503; I. G. Farbenindustrie A -G., Italian Patent 373,953; French Patent 793,226; British Patent 453,854.

[60] F. Hofmann and Otto, French Patent 632,768.

[61] I. G. Farbenindustrie A.-G., German Patent 545,397; British Patent 326,322; French Patent 682,055.

That carbon monoxide has a marked adverse effect on the reaction was observed by Otto.[55] As small a quantity as 0.75% of carbon monoxide reduced the rate of the reaction to such an extent that only 5 to 10 g. of the polymer of ethylene were obtained in a reaction similar to the one described above in which the yield was 85 to 95 g. More recent work has shown that carbon monoxide reacts with olefins in the presence of boron fluoride hydrates with the production of aliphatic carboxylic acids.[62] Similar condensations involving alcohols have been reported to take place at temperatures of 125° to 180°C. and under pressures greater than 25 atmospheres.[63]

As mentioned previously in connection with the gaseous olefins, the viscosities of the polymers vary according to the conditions of the polymerization. The viscosity decreases as the reaction is carried out at higher temperatures. This is especially true in polymerizations involving isobutylene. When catalytic quantities of boron fluoride are introduced into boiling isobutylene, the olefin polymerizes very rapidly to a water-white, thick oil. The product begins to boil at 200°C. and about 50% of it is distillable under 300°. At −80°, however, there is formed nearly quantitatively a solid polymer which has a molecular weight above 200,000.[64] The presence of ethylene and propylene do not affect the course of the reaction in any way, but when *n*-butylene and diisobutylene are added, the molecular weights of the polymers are much lower. In addition, diisobutylene causes a decrease in the yield.

Isobutylene and butadiene react in the presence of boron fluoride at −80°C. with the formation of a polymer which adds maleic anhydride at 200°. The product is a high boiling polycarboxylic acid which has a molecular weight of 2000.[65] The same type of reaction takes place between isobutylene and conjugated diolefins with polar substituents such as chlorine atoms.[66] In these polymerizations involving isobutylene and other substances of this type sulfur compounds and hydrogen fluoride poison the catalyst.[64]

The versatility of boron fluoride and its complex compounds as catalysts is shown by the fact that they not only effect the polymerization of olefins, but they also promote the cracking of hydrocarbon oils.[67]

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[62] E. I. du Pont de Nemours and Co., U. S. Patent 2,135,459.

[63] E. I. du Pont de Nemours and Co., U. S. Patent 2,170,825; British Patent 536,422.

[64] Thomas, Sparks, Frolich, Otto, and Mueller-Cunradi, *J. Am. Chem. Soc.*, 62, 276 (1940); U. S. Patents 2,049,062, 2,084,501, 2,109,772; Australian Patent 8861; Indian Patent 19,121; British Patent 401,297; see also I. G. Farbenindustrie A.-G., German Patent 704,038.

[65] Shell Development Co., Canadian Patent 379,134.

[66] Shell Development Co., Canadian Patent 381,742; *cf.* E. I. du Pont de Nemours and Co., British Patent 516,931.

[67] F. Hofmann and Wulff, German Patent 489,960.

It is evident from a consideration of all the work[68] involving the polymerization of olefins by boron fluoride catalysts that these reactions can be divided conveniently into the following two types: (*1*) The polymerization of olefins by boron fluoride alone, a process which is comparable to that involving aluminum chloride. Emphasis here should be placed on not only the unusual properties of the polymers obtained but also the fact that the catalytic activity of boron fluoride is not exhausted as is that of aluminum chloride during the course of the reaction. (*2*) The polymerization of olefins by coordinate complexes of boron fluoride, especially the complexes with water and with acetic acid. These reactions are comparable to those in which phosphoric acid is used as the catalyst.

The second type of polymerization process is commonly conducted under pressure at temperatures above 100 °C., under which conditions propylene polymerizes at a rapid rate. The olefin polymers produced boil at somewhat higher temperatures than those prepared in the presence of phosphoric acid; those resulting from reactions in the presence of boron fluoride dihydrate are of no practical use. The product produced by phosphoric acid, however, is primarily a mixture of isononylene and isodecylene—important intermediates for use in other condensation reactions. Diolefins and halogenated diolefins can be polymerized either alone or, as is more common in mixtures with monoolefins, in the presence of boron fluoride dihydrate at temperatures ranging from 0° to 35 °C.[69]

The mechanism of the polymerization reaction involving boron fluoride dihydrate is similar to that in which phosphoric acid is the catalyst. The olefin first adds to the catalyst, forming the boron fluoride alcoholate which then reacts at the moment it begins to break up into its components or reacts as such with other olefin molecules with the formation of the polymer. The way in which the reaction proceeds and the catalyst is continually regenerated is illustrated by Equation 14. Evidence for this formulation is found in the observation[70,71] that at higher temperatures boron fluoride dialcoholate catalyzes the decomposition of secondary alcohols with the formation of polymeric products. At 100 °C. the reaction between

$$BF_3\cdot 2H_2O + 2CH_3CH{=}CH_2 \rightleftharpoons$$

$$\begin{tikzcd} BF_3\cdot 2HO(CH_2)_2CH_3 \arrow[r, "2CH_3CH{=}CH_2"] & BF_3\cdot 2H_2O + 2C_6H_{12} \arrow[l, bend left, "2CH_3CH{=}CH_2"] \end{tikzcd} \quad (14)$$

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[68] For other references to the literature see Ellis, *The Chemistry of Synthetic Resins*, Reinhold, New York, 1935; see also Krczil, *Kurzes Handbuch der Polymerisationstechnik*, Akadem. Verlagsgesellschaft, Leipzig, 1941.

[69] E. I. du Pont de Nemours and Co., British Patent 516,931.

[70] Meerwein, *Ber.*, **66**, 411 (1933).

[71] Meerwein and Pannwitz, *J. prakt. Chem.*, **141**, 123 (1934).

2 kg. of isopropyl alcohol and 1.4 kg. of boron fluoride produced 1.2 kg. of a polymer mixture, of which 20% was isododecylene (b.p. 94° to 105°C. at 30 mm.).[72]

Other good catalysts which have been used for polymerizing olefins are phenyldiazonium borofluoride, $C_6H_5N_2BF_4$, and phenyltetrazonium diborofluoride, $C_6H_4(N_2BF_4)_2$.[73] Indene, styrene, cumarone, phenylbutadiene, and isoprene give amorphous, white powders in the presence of these catalysts. Turpentine and olefins from cracked paraffin hydrocarbons produce oils and colophony-like resins which are useful for coating materials. The reaction with rubber leads to the formation of gutta-percha- or leather-like products which have been used as insulating and coating materials. The volatility of these catalysts makes their elimination from the polymers quite easy, and under certain conditions spongy and porous products are obtained.

Boron fluoride and its complex compounds have also been found useful in the polymerization of vinyl compounds such as vinyl acetate, vinyl bromide, and α-bromoacylic ester.[74] These polymers have no particular advantages over those which have been obtained by the peroxide-catalyzed reaction.

Another field in which the catalytic effect of boron fluoride has been applied is that of the isomerization[75] and cyclization of olefins.[76] In the presence of boron fluoride *trans*-stilbene has been formed in 92.3% yield by the rearrangement of *cis*-stilbene. The reaction took place in 36 hours in ether solution, but it proceeded with a much greater velocity in carbon tetrachloride. In contrast to this, even after the addition of hydrogen bromide to diethyl maleate in the presence of boron fluoride or its dietherate, the extent of isomerization was less than 1%.

In the presence of 4 to 7% of boron fluoride-acetic acid the cyclization of rubber takes place in from 45 minutes to 3 hours at 130° to 140°C. Benzene and carbon tetrachloride have been employed as solvents for the reaction mixture, and the use of a purified petroleum fraction boiling at 150° to 190°C. has been particularly advantageous. The properties of the product depend on the extent to which the cyclization has been effected, varying from rubber-like, soft, easily torn masses to solid, leather-like polymers. The latter substances soften at 120°C., but do not have a softness comparable to that of rubber. Insoluble, horny cyclization products have also been prepared. The polymerized rubber still contains double bonds, the number of which also depends upon the extent of cyclization, and as a result the product can be vulcanized. The vulcanizates, which are hard masses similar to those from rubber itself, have been used to replace the oils in paints. They adhere firmly to glass, porcelain, and metal surfaces and show excellent fastness to water. In contrast to the oil varnishes such paints are permeable to moisture, but the pigments appear to be protected in such a way by the cyclized rubber that they are stable to alkali.

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[72] Whitmore and Laucius, *J. Am. Chem. Soc.*, 61, 973 (1939).

[73] Resinous Products and Chemical Co., U. S. Patent 1,892,101; see references cited in foot-notes 130 and 131 for the preparation and thermal decomposition of the diazonium borofluorides.

[74] Marvel and Riddle, *J. Am. Chem. Soc.*, 62, 2666 (1940).

[75] Price and Meister, *J. Am. Chem. Soc.*, 61, 1595 (1939).

[76] Stevens and Miller, *Proc. Rubber Tech. Conf., London*, 267 (1938); *Chem. Abstracts*, 32, 7771 (1938).

Not only olefins but also the paraffin hydrocarbons of low molecular weight are isomerized by boron fluoride in either the gaseous or liquid phase. Examples of such a reaction are the isomerizations of *n*-butane to isobutane and of *n*-pentane to isopentane in the presence of the catalyst at temperatures ranging from 10° to 290°C.[77] Boron fluoride also acts as a promoter for the aluminum bromide-catalyzed isomerization of *n*-butane.[78]

Some brief references in the patent literature would indicate that boron fluoride catalysts have been found somewhat useful in the alkylation of paraffin and cycloparaffin hydrocarbons by olefins. Boron fluoride hydrate has been used for the reaction between ethylene and isobutane, and a boron fluoride-hydrogen fluoride catalyst was used for the alkylation of methylcyclopentane with propylene.[79]

V. REACTIONS OF AROMATIC COMPOUNDS

1. Nuclear Alkylation

A. Alkylation of Hydrocarbons

In the discussion of the mechanism of the polymerization of olefins, it was pointed out that the olefin molecule reacted with another olefin molecule after being activated by the catalyst. If an aromatic hydrocarbon is present in the mixture, it is alkylated by the olefin in the presence of catalytic quantities of boron fluoride. As aromatic hydrocarbons are more reactive than olefins, the condensation is usually effected at lower temperatures than those required for the polymerization of olefins.

Hofmann and Wulff[80] have succeeded in replacing aluminum chloride by boron fluoride for catalysis of condensation reactions of the Friedel-Crafts type. Aromatic hydrocarbons such as benzene, toluene, tetralin, and naphthalene condensed with ethylene, propylene, isononylene,[81] and cyclohexene in the presence of boron fluoride with the production of the corresponding mono- or polyalkyl derivatives. The reaction took place whether hydrogen chloride was present in the mixture or not. The coordinate complexes of boron fluoride with hydroxy compounds, especially boron fluoride dihydrate and boron fluoride-diacetic acid, were also useful catalysts for such reactions.[81] Butenylbenzene has been prepared in a very satisfactory yield from butadiene and benzene in this way.

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[77] Standard Oil Development Co., U. S. Patent 2,216,221.

[78] Heldman, *J. Am. Chem. Soc.*, 66, 1786 (1944).

[79] The Texas Co., U. S. Patent 2,345,095; Universal Oil Products Co., U. S. Patent 2,340,557.

[80] F. Hofmann and Wulff, German Patent 513,414; British Patent 307,802; *cf.* I. G. Farbenindustrie A.-G., French Patent 665,812.

[81] I. G. Farbenindustrie A.-G., French Patent 799,016.

Careful studies on the alkylation of aromatic hydrocarbons have been described by Slannia, Sowa, and Nieuwland[82] and by Ipatieff and Grosse.[83] The work of Nieuwland showed that the velocity of the reaction between propylene and benzene increased with the strength of the acid with which the boron fluoride was coordinated to form the catalyst; thus, the rate increased with the use of the following acids in the order named: acetic, chloroacetic, dichloroacetic, trichloroacetic, and sulfuric. The catalyst was added to the reaction mixture as a solution of boron fluoride in the desired acid. The use of ether or ethyl acetate solutions of boron fluoride resulted in the formation of little or no isopropylbenzene.

When a solution of boron fluoride in sulfuric acid was added to catalyze the reaction, the quantities of mono- and diisopropylbenzene varied with the ratio of the weights of boron fluoride and sulfuric acid in the solution added to catalyze the reaction. The rate of propylation was not dependent on the temperature (0° to 80°C.) during the first hour. The catalyst was slowly destroyed during the course of the reaction, since the rate during the second hour was only about one-fourth that during the first hour. Furthermore, a catalyst which had been used would no longer effect the condensation reaction. As a result of this only a very small amount of triisopropylbenzene was obtained even in reactions in which 90% of the benzene had been converted into diisopropylbenzene. On the other hand, in the presence of a freshly added catalyst diisopropylbenzene was converted readily into tri- and tetraisopropylbenzenes. It was also shown that benzene and diisopropylbenzene do not react in the presence of boron fluoride-sulfuric acid even after being warmed.

When a catalyst prepared from boron fluoride and phenol was used, all the isopropylbenzenes up to the tetrasubstituted one were obtained, and there was no evidence of destruction of the catalyst. As was found in the case of the polymerization of olefins, propylene reacted more readily in these condensation reactions than did ethylene.

There is a fundamental difference between the action of boron fluoride and that of aluminum chloride. In the reaction catalyzed by boron fluoride, the product consisted of 98% of *p*-diisopropylbenzene and 2% of

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[82] Slannia, Sowa, and Nieuwland, *J. Am. Chem. Soc.*, **57**, 1547 (1935).

[83] Ipatieff and Grosse, *J. Am. Chem. Soc.*, **58**, 2339 (1936); *J. Org. Chem.*, **1**, 559 (1937).

o-diisopropylbenzene, while with the use of aluminum chloride the meta derivative was the main product according to Berry and Reid.[84] Any triisopropylbenzene formed in the reaction with aluminum chloride was primarily the symmetrical one.

In the condensation of propylene with benzene in the presence of boron fluoride dihydrate it is safe to make the same assumption as was done in the case of the polymerization of olefins that the first step is an addition of the catalyst to the double bond. The boron fluoride dialcoholate formed then reacts with benzene as such or at the instant of reversal of the reaction by which it was formed.

The fact that alcohols also condense with benzene in the presence of 0.3 to 1% of boron fluoride is in accord with this hypothesis. Both *n*- and isopropyl alcohols react with benzene in 9 hours at 60°C. with the production of cumene.[85] This fact would suggest that the condensation reaction probably proceeds by cleavage of the boron fluoride dialcoholate into boron fluoride dihydrate and the olefin which adds to benzene in the nascent state (possibly at the moment of decomposition). Since secondary and tertiary alcohols usually can be dehydrated more easily than the primary ones, they condense much more readily than the primary alcohols with benzene.

The alkylation of benzene in the presence of boron fluoride, especially by primary alcohols, is strongly accelerated by the addition of certain dehydrating agents such as phosphorus pentoxide, sulfuric acid, and benzenesulfonic acid.[86] Benzene and *n*-butyl alcohol (0.5 mole) in the presence of boron fluoride (0.5 mole) gave no butylbenzene in 4 hours, but after addition of 0.12 mole phosphorus pentoxide there was obtained in 3 hours a 73.5% yield of *sec*-butylbenzene and 8.3% of *p*-di-*sec*-butylbenzene. Addition of 0.5 mole 100% sulfuric acid yielded 37.4% of *sec*-butylbenzene, and 0.5 mole benzenesulfonic acid afforded 63.0% of *sec*-butylbenzene in 4 hours. In the same way alcohols containing up to 12 carbon atoms were made to react with benzene. Methanol and ethanol, however, did not condense with benzene under these conditions, but benzyl alcohol produced diphenylmethane and *p*-dibenzylbenzene even without the addition of phosphorus pentoxide, sulfuric acid, or benzenesulfonic acid. The condensation of unsaturated alcohols with benzene is illustrated by that of allyl alcohol from which were obtained 31.1% of diphenylpropane and 8.7% of allylbenzene.

In cases in which dialkylbenzenes were formed by reactions with alcohols, only para derivatives could be isolated. The preparation of *p*-dialkylbenzenes was carried out effectively by subjecting alkylbenzenes to this reaction. Compounds in which both alkyl groups were the same could be obtained by a one-step reaction, but the yields were better if the alkylation was done in two steps.[87]

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[84] Berry and Reid, *J. Am. Chem. Soc.*, **49,** 3142 (1927).
[85] McKenna and Sowa, *J. Am. Chem. Soc.*, **59,** 470 (1937).
[86] Toussaint and Hennion, *J. Am. Chem. Soc.*, **62,** 1145 (1940).

The original method without the use of dehydrating agents[85] has been used for the alkylation of the xylenes by *tert*-butyl alcohol.[88] Boron fluoride is particularly desirable for this purpose, since it does not promote the migration of alkyl groups.

The method of alkylation of benzene derivatives by alcohols in the presence of boron fluoride and phosphorus pentoxide has also been of value for the preparation of *p*-alkyl phenyl halides. It is superior to alkylations involving aluminum chloride catalysis, since no halogen migrations and no meta substitution take place. The yields decrease with increasing molecular weight of the alcohol or phenyl halide and with increasing tendency of the alcohol to dehydrate.[89]

Naphthalene may be alkylated by alcohols in the presence of boron fluoride under similar conditions to those used for reactions with benzene.[90] In reactions with isopropyl alcohol, cyclohexanol, and *tert*-butyl alcohol the β-substituted naphthalenes were obtained in reasonably good yields (35% β-isopropylnaphthalene, 63% β-cyclohexylnaphthalene, 62% β-*tert*-butylnaphthalene), but the condensation with benzyl alcohol gave mainly α-benzylnaphthalene (28%) along with small quantities of the β derivative. The polyalkylation of naphthalene by alcohols can take place as an excess of isopropyl alcohol (4 moles to 1 mole of naphthalene) produced a 57% yield of triisopropylnaphthalene. In the reactions already mentioned involving cyclohexanol, *tert*-butyl alcohol, and benzyl alcohol low yields of the polyalkylnaphthalenes were isolated (9% dicyclohexylnaphthalene, 5% di-*tert*-butylnaphthalene, 15% dibenzylnaphthalene, 2% tribenzylnaphthalene).

Since benzyl alcohol is unable to lose water with the formation of an olefin and cyclohexanol has no tendency to form hexene under the conditions of the condensation, Price and Ciskowski suggested that in these cases the boron fluoride merely weakens the carbon-oxygen bond of the alcohol. At first they thought that the alkyl group tended to split off in the form of an alkyl cation which reacted with the aromatic nucleus. An analogous explanation was advanced for the activation of olefins by boron fluoride alone in alkylations involving them.

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[87] Welsh and Hennion, *J. Am. Chem. Soc.*, **63**, 2603 (1941); Hennion and Auspos, *ibid.*, **65**, 1603 (1943).

[88] Nightingale, Radford, and Shanholtzer, *J. Am. Chem. Soc.*, **64**, 1662 (1942); Nightingale and Janes, *ibid.*, **66**, 154 (1944).

[89] Hennion and Pieronek, *J. Am. Chem. Soc.*, **64**, 2751 (1942).

[90] Price and Ciskowski, *J. Am. Chem. Soc.*, **60**, 2499 (1938).

Later evidence, however, proved that the reaction does not involve an olefin intermediate, since the alkylation of benzene by an optically active *sec*-butyl alcohol in the presence of boron fluoride produced an optically active product. When aluminum chloride was used as catalyst in this reaction, a racemized product was isolated. Production of the asymmetric *sec*-butylbenzene tended to eliminate the positive ion mechanism suggested earlier, and Price and Lund have proposed that the activation effect of boron fluoride is merely one of polarization of the carbon-oxygen bond by complex formation.[91] The alkyl ion mechanism has not been definitely excluded, however.[92,93]

Alkylations of the Friedel-Crafts type with alkyl halides have been catalyzed by boron fluoride. Cyclohexyl fluoride alkylated toluene in a vigorous reaction in the presence of boron fluoride, but alkyl chlorides and bromides did not react when the catalyst was boron fluoride alone.[92,93] The addition to the mixture of polar compounds reactive to boron fluoride effected the rapid condensation of many active halides with benzene in moderately good yields.[94] The best yields were obtained from the tertiary halides, poorer yields resulted from the secondary compounds, and the primary halides for the most part did not react at all. Allyl chloride reacted but the yield was quite poor.

The boron fluoride complexes of the ethers decompose easily with the formation of olefins or their polymers[70,71] in much the same way as do those of the secondary alcohols, and as a result the condensation of ethers with benzene in the presence of boron fluoride has been accomplished.[95] By the use of this reaction secondary alkylbenzenes have been obtained from *n*-alkyl ethers and tertiary alkylbenzenes from ethers containing secondary alkyl groups (in so far as their structures allow it). A consideration of the products formed indicates that the condensation involves the formation of olefin intermediates. Phenyl isopropyl and benzyl ethyl ethers react explosively, diisopropyl and dibenzyl ethers condense with less violence, and diethyl, diisoamyl, and di-*n*-amyl ethers undergo the reaction with benzene only at higher temperatures. The dialkylbenzenes, which are formed as by-products in these reactions, are the ortho and para derivatives, with the latter predominating. Naphthalene reacts with boron fluoride etherates in the same way as does benzene.[96] By refluxing a mixture of naphthalene (1 mole) and excess boron fluoride-methyl ether (4 moles) a mixture of polymethylnaphthalenes is obtained.

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[91] Price and Lund, *J. Am. Chem. Soc.*, 62, 3105 (1940).

[92] Burwell, Jr., and Archer, *J. Am. Chem. Soc.*, 64, 1032 (1942).

[93] Petrov, *J. Gen. Chem. U. S. S. R.*, 10, 981 (1940); *Chem. Abstracts*, 35, 3603 (1941).

[94] Hennion and Kurtz, *J. Am. Chem. Soc.*, 65, 1001 (1943).

[95] O'Connor and Sowa, *J. Am. Chem. Soc.*, 60, 125 (1938).

[96] Kolka and Vogt, *J. Am. Chem. Soc.*, 61, 1463 (1939).

The reaction is not limited to simple aliphatic ethers; cyclic ethers of the ethylene oxide type (ethylene, propylene, and butylene oxides) condense with aromatic hydrocarbons in the presence of boron fluoride with the production of alcohols.[97] In this way phenylethyl alcohol and diphenylethane have been obtained by the reaction between benzene and ethylene oxide. This type of reaction of the cyclic ethers, which usually has been carried out by means of aluminum chloride, should also be applicable to the aliphatic and cycloparaffin hydrocarbons.

The alkylation of benzene by esters is also catalyzed by boron fluoride.[98] The amount of boron fluoride ($^1/_{70}$ to 1 mole) and the conditions of the condensation depend on the ester used. Some reactions are complete after the material has stood at room temperature overnight, while others require refluxing from 30 minutes to as long as 20 hours. There is evidence that this reaction proceeds via an olefin intermediate, since normal and secondary butyl esters (formate, acetate, phosphate, sulfate) yield *sec*-butylbenzene and isobutyl formate produces *tert*-butylbenzene. Also, the normal alkyl esters react with considerably more reluctance than do the corresponding iso esters, since the formation of an olefin by the cleavage of the normal esters is more difficult. For similar reasons condensations involving formate esters proceed much more easily than those with acetates and benzoates, which appear to be most unreactive.

In the condensation of benzene with esters in the presence of boron fluoride the second alkyl group is introduced primarily in the para position, but a little of the ortho derivative is also formed. Vinyl acetate reacts vigorously with benzene, but only indefinite resinous products are produced.

Cracking of paraffin hydrocarbons with the simultaneous recombination of the olefin fragments to produce aromatic hydrocarbons is not possible over boron fluoride. The only catalysts which have been successfully used for this purpose are the chlorides of aluminum and zirconium.[99]

B. Alkylation of Phenolic Derivatives and Amines

The alkylation of phenols, phenol ethers, and phenolcarboxylic acids by olefins is catalyzed by boron fluoride and its complex compounds, but in contrast to the reaction with the aromatic hydrocarbons there are two possible ways in which the reaction may proceed. The olefin may react with the phenolic compound either by direct nuclear condensation, or it may form a phenol ether which rearranges subsequently. Which mechanism is more prevalent in a given reaction is determined by the conditions employed.

[97] I. G. Farbenindustrie A.-G., British Patent 354,992; French Patent 716,604.

[98] McKenna and Sowa, *J. Am. Chem. Soc.*, 59, 1204 (1937).

[99] Grosse and Ipatieff, *J. Am. Chem. Soc.*, 57, 2415 (1935).

The alkylation of phenols was described first by Hofmann and Wulff,[100] who have shown that phenols condense with ethylene at elevated temperatures and pressures in the presence of 5% of boron fluoride and 2% of hydrogen chloride. By varying the conditions of the reaction it was possible to obtain either phenol ethers or nuclearly alkylated phenols. Other olefins such as propylene, butylene, diisobutylene, isononylene, isododecylene, and cyclohexene also reacted with phenol in the same way. The reaction was effected at 100°C. most successfully with complexes of boron fluoride and especially boron fluoride dihydrate.

The dependence of the propylation of phenol on the temperature and duration of the reaction and on the relative proportions of propylene and boron fluoride has been investigated by Sowa, Hinton, and Nieuwland.[101] The products obtained at various temperatures and by progressive propylation of the initial condensation products are indicated in Reactions 15. The

$$C_6H_5OH + CH_3CH{=}CH_2 \xrightarrow[\text{A little at 20°C.}]{\text{0°C.}} \underset{\text{Phenyl isopropyl ether}}{C_6H_5OC_3H_7\text{-}i} \tag{15a}$$

$$C_6H_5OC_3H_7\text{-}i \xrightarrow[\text{A little at 0°}]{\text{20°}} \underset{\text{2-Isopropylphenol}}{i\text{-}C_3H_7C_6H_4OH} \tag{15b}$$

$$i\text{-}C_3H_7C_6H_4OH + C_3H_6 \xrightarrow[\text{A little at 20°}]{} \underset{\text{2-Isopropylphenyl isopropyl ether}}{i\text{-}C_3H_7C_6H_4OC_3H_7\text{-}i} \tag{15c}$$

$$i\text{-}C_3H_7C_6H_4OC_3H_7\text{-}i \xrightarrow[\text{A little at 20°}]{} \underset{\text{2,4-Diisopropylphenol}}{(i\text{-}C_3H_7)_2C_6H_3OH} \tag{15d}$$

$$(i\text{-}C_3H_7)_2C_6H_3OH + C_3H_6 \xrightarrow{\text{20°}} \underset{\text{2,4-Diisopropylphenyl isopropyl ether}}{(i\text{-}C_3H_7)_2C_6H_3OC_3H_7\text{-}i} \tag{15e}$$

$$(i\text{-}C_3H_7)_2C_6H_3OC_3H_7 \xrightarrow[\text{A little at 20°}]{} \underset{\text{2,4,6-Triisopropylphenol}}{(i\text{-}C_3H_7)_3C_6H_2OH} \tag{15f}$$

$$(i\text{-}C_3H_7)_3C_6H_2OH + C_3H_6 \xrightarrow[\text{A little at 20°}]{\text{40°}} \underset{\text{2,4,6-Triisopropylphenyl isopropyl ether}}{(i\text{-}C_3H_7)_3C_6H_2OC_3H_7\text{-}i} \tag{15g}$$

products of reactions 15a to 15f were formed by carrying out the condensations in solution in benzene, but the 2,4,6-triisopropylphenyl isopropyl ether was obtained by introducing propylene into pure phenol in the presence of boron fluoride.

A study of the rearrangement of phenyl isopropyl ether was also carried out by Nieuwland and co-workers.[102] By dissolving 3% of boron fluoride in 250 g. of phenyl isopropyl ether without cooling the solution, the following products were obtained: 90 g. of phenol, 34 g. of 2-isopropylphenol, 44 g. of 2,4-diisopropylphenyl isopropyl ether, 12 g. of 2,4,6-triisopropylphenyl isopropyl ether, and traces of phenyl isopropyl ether and 2-isopropylphenyl isopropyl ether. 2,4,6-Triisopropylphenyl isopropyl ether was recovered unchanged after further treatment with boron fluoride; however, phenol can be propylated very easily by the ether-boron fluoride mixture, the ether losing its *O*-isopropyl group in the process. A small amount of phenol, some of the ether, and all the possible substituted phenols and ethers up to and including 2,4,6-triisopropylphenol were isolated. When 2,4,6-triisopropylphenol was warmed with phenol and boron fluoride, only about half of each of the starting materials was recovered. The rest of the material was converted into 2-isopropylphenol and 2,4-diisopropylphenol.

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[100] F. Hofmann and Wulff, German Patent 604,867.

[101] Sowa, Hinton, and Nieuwland, *J. Am. Chem. Soc.*, **54**, 3694 (1932).

[102] Sowa, Hinton, and Nieuwland, *J. Am. Chem. Soc.*, **54**, 2019 (1932); **55**, 3402 (1933).

An analogous cleavage of a nuclear propenyl group by boron fluoride had been observed previously by Landolph in the case of anethole.[103] The product obtained was a mixture of anisole and a substance with a higher carbon content.

The reaction between methyl chavicol and boron fluoride etherate has recently been shown to give metanethole, a dimer of anethole, exclusively.[104] Thus no cleavage of the alkene side chain took place in this case. It is of interest also that in connection with this work the Beckmann rearrangement of the oximes of benzophenone and of ω-*p*-methoxybenzoylbutyric acid was effected by boron fluoride etherate.

The rearrangement of cresol ethers takes place in a similar way to that of the phenyl ethers, the isopropyl group migrating to the positions ortho and para to the hydroxyl group. Anisole is not rearranged by boron fluoride, but an isopropyl group is easily introduced into the nucleus by propylene.

On the basis of the data obtained on the alkylation and rearrangement of the phenols and their ethers, certain conclusions have been reached regarding the mechanism of the reaction. Any conclusions regarding whether the reaction pursues an inter- or intramolecular course are undoubtedly speculative, but it has been established that propylene can be introduced directly into the nucleus of phenyl ethers, since anisole, which cannot rearrange, is alkylated by propylene.

Unsaturated fatty acids and their esters, such as the products known to the varnish industry as lithographic oils, also condense with phenols in the presence of boron fluoride catalysts in the same way as do the olefins.[105] The alkylation of phenols and phenol ethers by natural resinous materials in the presence of boron fluoride has been considered as a means of improving the natural products. Colophony-abietic acid and dammar copal and their esters have been condensed in 20 hours with phenols and phenol ethers at 30° to 40°C.[106] The condensation products obtained in this way differed considerably from the starting materials in physical and chemical properties. They showed a marked decrease in the iodine number, an increased acetyl number, usually showed a higher softening point, and with them the Storch-Morawski reaction characteristic of the resin acids and colophony was negative. The use of other condensing agents such as aluminum chloride, zinc chloride, or sulfuric acid also leads to condensation products, but they are of no use in the varnish industry. When anisole is used in the condensation reaction in place of phenol, no cleavage of the ether linkage takes place.

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[103] Landolph, *Compt. rend.*, **86**, 602 (1878); *Ber.*, **13**, 144 (1880).

[104] van der Zanden, de Vries, and Dijkstra, *Rec. trav. chim.*, **61**, 280 (1942).

[105] I. G. Farbenindustrie A.-G., German Patent 615,530.

Styrene polymers can be improved by mixing 10% of a phenol ether with the styrene and carrying out the polymerization with boron fluoride-acetic acid.[107]

The method of alkylating aromatic hydrocarbons by the use of alcohols and ethers has also been applied to the phenols.[108,109] When molar quantities of *n*-propyl or isopropyl alcohol and phenol were refluxed with 35 mole per cent of boron fluoride for 1 hour, the temperature of the mixture rose from 115° to 160°C. The product from the reaction with isopropyl alcohol consisted of the following components: 2,4-diisopropylphenyl isopropyl ether (11%), 2-isopropylphenol (28%), and 4-isopropylphenol (20%). With *n*-propyl alcohol there were isolated the same compounds in similar yields (13%, 32%, and 16% respectively). Thus, with both *n*-propyl and isopropyl alcohols only the isopropylphenols were formed, as was the case in other condensations with boron fluoride. Methanol and ethanol, in contrast to the behavior of the propyl alcohols, did not react with phenol when refluxed with it in the presence of 21% of boron fluoride. By heating the reaction mixture to 170°C. for 3 hours, anisole was obtained in a 58% yield (phenetole in a 17% yield, when ethanol was used). Small amounts of alkyl phenyl ethers were also formed.

Higher reaction temperatures are also necessary for the alkylation of phenols by the boron fluoride complexes with dimethyl and diethyl ether. Phenol and anisole were methylated by prolonged refluxing (2 to 32 hours) with the methyl ether-boron fluoride complex,[96] which was prepared by heating boron fluoride-methanol for 3 hours.[48] The reaction continued until pentamethylanisole was formed. The reaction between phenol and boron fluoride etherate at 200°C. gave a 26% yield of phenetole in 3 hours. Various ethylphenols and ethyl phenyl ethers were produced as by-products.[109]

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[106] I. G. Farbenindustrie A.-G., German Patents 581,956, 605,688, 582,846, and 628,660.

[107] I. G. Farbenindustrie A.-G., German Patent 674,984.

[108] Sowa, Hennion, and Nieuwland, *J. Am. Chem. Soc.*, **57**, 709 (1935).

[109] Hennion, Hinton, and Nieuwland, *J. Am. Chem. Soc.*, **55**, 2857 (1933).

The alkylation of the phenolcarboxylic acids represents a further application of the reaction involving olefins. Croxall, Sowa, and Nieuwland[110] have induced propylene to react with salicylic acid suspended in heptane in 3 days. The reaction was carried out under a pressure of 8 to 10 cm. above atmospheric pressure, and 22.3 mole per cent of boron fluoride was added to catalyze the condensation. The first product of the reaction was isopropyl salicylate, which rearranged subsequently and formed 2-hydroxy-3-isopropylbenzoic acid. As more propylene was dissolved in the reaction mixture, this acid was esterified, and the ester isopropyl group migrated to the nucleus with the production of 2-hydroxy-3,5-diisopropylbenzoic acid, which was esterified by reaction with propylene. 2-Hydroxy-5-isopropylbenzoic acid was isolated only in very small quantities. No propoxy derivatives of salicylic acid were formed.

The heating of isopropyl salicylate alone to 130° to 140°C. in the presence of boron fluoride resulted in the formation of 2-hydroxy-3-isopropylbenzoic acid, 2-hydroxy-3,5-diisopropylbenzoic acid, and traces of 2-hydroxy-5-isopropylbenzoic acid. Since isoalkylsalicylic acids were obtained from the salicylate esters of *n*-propyl, isopropyl, and *n*-butyl alcohols, it was assumed that the alkylation proceeds via an olefin intermediate. Other evidence for this was the production of *tert*-butylsalicylic acid from the isobutyl ester,[111] and the fact that some free salicylic acid was isolated. It is of interest to note that while the isopropyl and *sec*-butyl salicylates rearranged predominantly with the alkyl group entering the position ortho to the hydroxyl group, the *tert*-butyl group migrated to the para position.

The reaction of propylene with *p*-hydroxybenzoic acid in the presence of boron fluoride was quite different.[112] In this case the etherification of the phenolic hydroxyl group was the initial reaction; no isopropyl *p*-hydroxybenzoate could be isolated. The ether then rearranged, with the alkyl group migrating to the position ortho to the hydroxyl group. Even upon treatment of isopropyl *p*-hydroxybenzoate by boron fluoride the *p*-isopropoxy compound was formed first before further reaction took place. These observations led to the conclusion that a direct migration into the nucleus of an isopropyl group attached to the carboxyl group was not possible; the initial reaction of the ester seemed to be a rearrangement to the isopropoxy derivative, followed by a shift of the isopropyl group to the nucleus, with the production of 3-isopropyl-4-hydroxybenzoic acid. This does not rule out the possibility of a direct nuclear propylation of the *p*-hydroxybenzoic acid, such as that which has been shown to be possible in the case of anisole.

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[110] Croxall, Sowa, and Nieuwland, *J. Am. Chem. Soc.*, 56, 2054 (1934).
[111] Croxall, Sowa, and Nieuwland, *J. Org. Chem.*, 2, 253 (1937).
[112] Croxall, Sowa, and Nieuwland, *J. Am. Chem. Soc.*, 57, 1540 (1935).

The treatment of a carbon tetrachloride solution of *m*-hydroxybenzoic acid by propylene and boron fluoride led to the production of 3-isopropoxybenzoic acid, 4-isopropyl-3-isopropoxybenzoic acid, and some isopropyl *m*-hydroxybenzoate. It is probable that in this case both etherification and esterification took place simultaneously. The main product from the rearrangement of both the isopropyl ether and isopropyl ester of *m*-hydroxybenzoic acid was 3-hydroxy-4-isopropylbenzoic acid. The rearrangement of the ether also afforded some 3-isopropoxy-4-isopropylbenzoic acid, and other products obtained from the ester were 3-isopropoxy-4-isopropylbenzoic acid, its isopropyl ester, 3-isopropoxybenzoic acid, and *m*-hydroxybenzoic acid.

The isopropyl group of the salicylic ester migrates directly into the nucleus under the influence of boron fluoride and that of the *m*-hydroxybenzoic ester moves directly into the nucleus for the most part, while that of the *p*-hydroxybenzoic ester rearranges first to the *p*-hydroxy group before entering the nucleus. The fact that salicylic acid does not form an ether with propylene is in accord with the general observation that ethers of *o*-hydroxy compounds and particularly *o*-hydroxy acids and ketones are very difficult to prepare.

As would be expected, alcohols as well as olefins react with salicylic acid in the presence of boron fluoride, with the formation of esters; nuclearly substituted alkylsalicylic acids are also formed in reactions with *sec*- and *tert*-butyl alcohols.[111] This condensation probably takes place with the formation of olefin intermediates, since *n*-butyl alcohol gives *sec*-butyl derivatives, and *tert*-butyl alcohol affords isobutyl derivatives. When benzene and diphenyl ether are present in the reaction mixture, they undergo alkylation.

Aromatic amines such as aniline and *N*-alkylanilines are not alkylated by olefins in the presence of boron fluoride. These amines are so basic that the catalyst combines with them immediately and is no longer free to catalyze condensation reactions. On the other hand, boron fluoride dihydrate catalyzes the alkylation of weakly basic amines, such as diphenylamine, by diisobutylene.[113] The products formed by the reaction are *p*-diisobutyl- and *p,p*′-diisobutyldiphenylamine.

2. Introduction of Negative Substituents

A. Acylation, Nitration, and Sulfonation Reactions

Aluminum chloride can be replaced by boron fluoride for use in catalyzing Friedel-Crafts reactions. Benzene and toluene do not react with acetic anhydride as smoothly in the presence of boron fluoride as they do with aluminum chloride (the yields of acetophenone and *p*-methylacetophenone are 13.7 and 70.9% respectively[70,114]), but anisole and acetic anhydride form *p*-methoxyacetophenone in a 95% yield.[70,114,115] Fluorescein is formed in an almost theoretical yield by refluxing a benzene solution of phthalic anhydride, resorcinol, and boron fluoride, and the substitution of phenol for resorcinol in the reaction mixture produces phenolphthalein in a 72% yield. These condensations are not accelerated by the addition of hydrofluoric acid,[114] while the activity of aluminum chloride is increased by hydrochloric acid.

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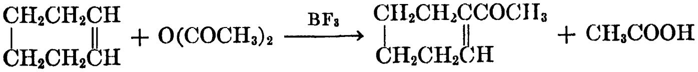
[113] Kästner, unpublished work.

Boron fluoride does not effect the condensation of dimethylaniline with acetic anhydride for the same reason as that mentioned previously. The tendency for formation of the boron fluoride-dimethylaniline complex is so great that the boron fluoride is not available for catalysis.[114]

Cyclohexene has been condensed with acetic anhydride in the presence of boron fluoride with the formation of 2-acetylcyclohexene in a 27% yield (Eq. 16). In the same way α,β-unsaturated ketones were prepared by the reaction of diisobutylene, isononylene, and isododecylene with acetic anhydride in the presence of boron fluoride or its dihydrate.[116] These condensations were carried out at temperatures ranging from 0°C. to room temperature. Molar quantities of boron fluoride were required for this reaction, since the catalyst combines with the ketones which are formed and is then unavailable for catalysis.



$$\begin{array}{l}CH_2CH_2CH\\ |\qquad\qquad \|\\ CH_2CH_2CH\end{array} + O(COCH_3)_2 \xrightarrow{BF_3} \begin{array}{l}CH_2CH_2CCOCH_3\\ |\qquad\qquad \|\\ CH_2CH_2CH\end{array} + CH_3COOH \qquad (16)$$

There is no particular advantage in using boron fluoride in these condensations instead of the usual catalysts (aluminum and zinc chlorides), since the condensation of acetic anhydride with itself occurs as a side reaction (see Section VI).

A much simpler method of preparing ketones consists of saturating a solution of the phenol[70,117] or phenol ether[117] in double the molar quantity of a fatty acid with boron fluoride. The container is then sealed and warmed for 0.5 to 2 hours at about 70°C., and the reaction mixture is decomposed with sodium acetate.

By the use of this method 91% of *p*-hydroxyacetophenone and 5.9% of *o*-hydroxyacetophenone were obtained from phenol and acetic acid, 83.7% of *p*-hydroxypropiophenone and 8.7% of *o*-hydroxypropiophenone from phenol and propionic acid, 97.0% of 2-acetyl-4,6-dimethylphenol (I) from 2,4-dimethylphenol and acetic acid, and 90.6% of *p*-methoxyacetophenone was formed from anisole and acetic acid. By increasing the reaction time to 16 hours, 48.5% of I and 21.5% of 3-acetyl-4,6-dimethylanisole (II) were produced from 2,4-dimethylanisole and acetic acid.

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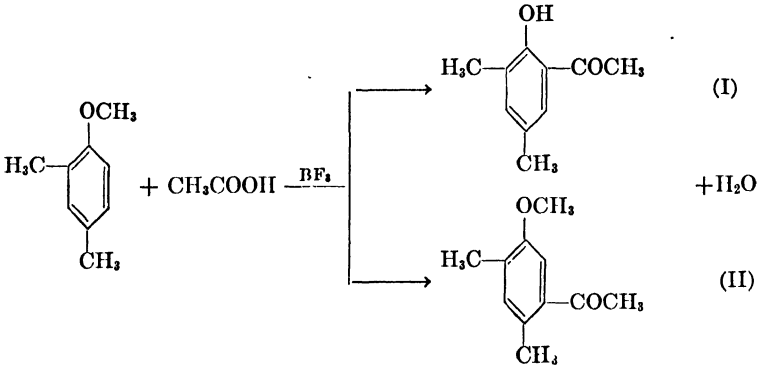
[114] Meerwein and Vossen, *J. prakt. Chem.*, **141**, 149 (1934).

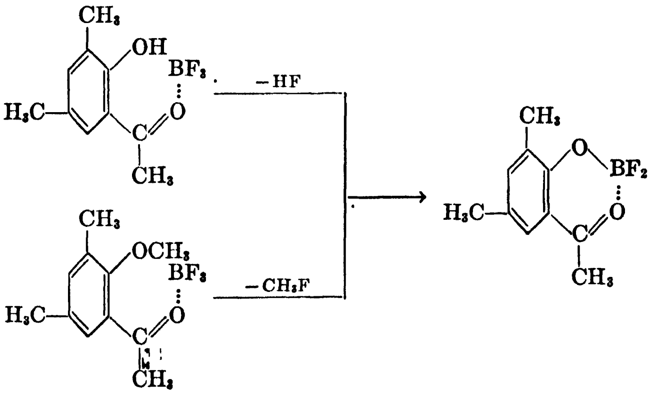
[115] Maier-Hüser, Thesis, Marburg, 1933, p. 27.

[116] I. G. Farbenindustrie A.-G., unpublished work; see also I. G. Farbenindustrie A.-G., U. S. Patent 2,210,837.

[117] Kästner, Thesis, Marburg, 1937.

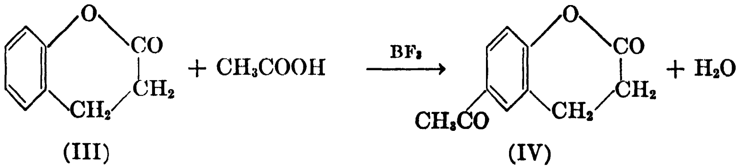


In none of these condensations with boron fluoride as the catalyst has the presence of hydrogen fluoride or fluoromethane been observed in the reaction mixture[70,117] in those cases in which the keto group enters the para or the meta position. Reactions with boron fluoride differ from those with aluminum chloride, therefore, since with the latter catalyst the condensations take place with the elimination of hydrogen chloride and phenol ethers are easily cleaved. Only in the case in which the keto group enters the position ortho to the hydroxy or methoxy group is hydrogen fluoride or fluoromethane formed. Very stable inner complexes are the result of an intramolecular reaction (Eq. 17) between the ortho methoxy or hydroxy group and the boron fluoride complex of the acyl group produced in the reaction.



(17)

The nuclear acylation of phenyl esters by boron fluoride catalysis is considerably more difficult than the reaction with phenols and their ethers. Under the same conditions under which anisole gives *p*-methoxyacetophenone in an excellent yield 3,4-dihydrocoumarin (III) affords only a 1.8% yield of 6-acetylhydrocoumarin (IV).[117]



Boron fluoride has been found to be quite effective for the catalysis of the sulfonation and nitration of aromatic compounds.[118] The water formed in the reaction is removed by the formation of boron fluoride hydrate, as is illustrated in Equations 18.

$$\begin{aligned} RH + H_2SO_4 + BF_3 &\longrightarrow RSO_3H + BF_3 \cdot H_2O \\ RH + HNO_3 + BF_3 &\longrightarrow RNO_2 + BF_3 \cdot H_2O \end{aligned} \qquad (18)$$

When boron fluoride is present, an excess of sulfuric or nitric acid is unnecessary for the sulfonation or nitration of aromatic compounds. It also offers the advantage that the reactions proceed at lower average temperatures (40° to 100°C.) and at increased velocities (the average reaction time is 0.5 to 1 hour), and products of higher purity are obtained in better yields than are given by the usual methods. It is obvious from the above equations that an equivalent quantity of boron fluoride is necessary. By the addition of a sufficient quantity of water to convert all the boron fluoride monohydrate to the dihydrate, the catalyst can be recovered in a good yield (50 to 90%) by distillation. The following sulfonic acids were obtained by the sulfonation of the corresponding hydrocarbons with 94% sulfuric acid (the yields are in parentheses): benzenesulfonic acid (98%), *p*-toluenesulfonic acid (98%), *p*-phenolsulfonic acid (73%), and carbazolesulfonic acid (95%). By sulfonating naphthalene at 30°C., a 94% yield of α-naphthalenesulfonic acid was obtained, but at 160°C. the β acid (93%) was isolated along with a small amount (5%) of β,β′-dinaphthyl sulfone. Biphenyl produced both the mono- and disulfonic acids in yields of 27% and 67%, respectively.

Boron fluoride does not accelerate the sulfonation of all aromatic compounds, and it has no advantages as a catalyst in the sulfonation of chlorobenzene, nitrobenzene, and benzoic acid. It does have considerable value, however, in the nitration of compounds containing negative groups.

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[118] Thomas, Ancilotti, and Hennion, *Ind. Eng. Chem.*, 32, 408 (1940).

In reactions with molar quantities of boron fluoride and 92% nitric acid, nitrobenzene gave an 87% yield of *m*-dinitrobenzene, benzoic acid yielded 82% of *m*-nitrobenzoic acid, and methyl benzoate afforded 77% of the *m* nitro derivative. The nitration of *p*-toluenesulfonic acid and of phthalic anhydride gave 2-nitro-4-methylbenzenesulfonic acid (92%) and 3-nitrophthalic acid (87%), respectively.[119]

Sulfonations of α- and β-naphthylamines and of β-naphthol were carried out in order to determine whether the boron fluoride-amine complex would exert any unusual directive influence. No unusual effects were noted, and in the case of the α derivative, naphthionic acid was obtained in an excellent yield (86%). β-Naphthylamine was sulfonated quantitatively at several temperatures with the production of the 5- and 8-sulfonic acids, of which the 5 derivative predominated at higher temperatures. The sulfonation of β-naphthol produced the 3,6-disulfonic acid.[120]

The sulfonation and nitration reactions can be carried out successively in the presence of boron fluoride, without the isolation of the pure sulfonic acid being necessary. Benzene and toluene are sulfonated by the addition of molar quantities of sulfuric acid and boron fluoride. After the sulfonation is complete, the addition of molar quantities of fresh boron fluoride and fuming nitric acid converts the sulfonic acids to *m*-nitrobenzenesulfonic acid (80%) and 2-nitro-4-methylbenzenesulfonic acid (82%).

B. Fries Rearrangement

The condensation of phenols with organic acids is not necessarily a direct nuclear substitution. If the reaction time is shortened from 2 hours to 20 minutes in the condensation of 2,4-dimethylphenol with acetic acid in the presence of boron fluoride, along with the 2-acetyl-4,6-dimethylphenol (20.7%) expected, there is isolated 41.6% of 2,4-dimethylphenyl acetate.[117] This indicates that the acylation of the phenol proceeds primarily by way of the phenyl ester which is subsequently rearranged. Aluminum chloride is usually used in the reaction generally known as the *Fries rearrangement*, but the mechanism of the rearrangement has been studied advantageously with boron fluoride as the catalyst.[70,117] The boron fluoride complexes of the phenyl esters and phenol ketones crystallize very well and dissolve readily in nitrobenzene, boron fluoride-acetic acid, boron fluoride etherate, and chlorobenzene. Thus, it is possible to carry out a rearrangement with well defined compounds which are easily identified and to follow the reaction in a homogeneous medium both from a kinetic and preparative view-point.

The rate of the rearrangement of boron fluoride-phenyl acetate into o- and p-hydroxyacetophenones varies with the solvent used; it is least in chlorobenzene and increases progressively as the reaction is carried out in boron fluoride etherate, nitrobenzene, and boron fluoride-acetic acid. At 70° to 73°C. the rearrangement of boron fluoride-phenyl acetate to p-hydroxyacetophenone is 51.1% complete in 7 hours in boron fluoride etherate solution, 52.7% complete in 80 minutes in nitrobenzene, and 89.5% complete in 80 minutes in boron fluoride-acetic acid. By following the kinetics of the rearrangement of 0.2 molar solutions of the boron fluoride-ester complex in the same solvents at 20°, a similar relationship has been observed.

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[119] E. I. du Pont de Nemours and Co., U. S. Patent 2,314,212.

[120] Hennion and Schmidle, *J. Am. Chem. Soc.*, 65, 2468 (1943).

TABLE IV

Rearrangement of Phenyl Esters

Ester	Reaction temperature, °C.	Product	Yield, %
Phenyl acetate	77.5	p-Hydroxyacetophenone	85.0
		o-Hydroxyacetophenone	10.0
p-Cresyl acetate	85 5	2-Hydroxy-5-methylacetophenone	57.9
2,4-Dimethylphenyl acetate	81	2-Acetyl-4,6-dimethylphenol	77.5
2,5-Dimethylphenyl acetate	101	4-Acetyl-2,5-dimethylphenol	84.8

Phenyl esters of aliphatic acids containing more than 10 carbon atoms also rearrange to the corresponding phenol ketones in the same way.[121]

No p-hydroxybenzaldehyde is obtained by the rearrangement of phenyl formate by boron fluoride, because the aldehyde group of the p-hydroxybenzaldehyde formed in the reaction condenses with the phenol which results from the decomposition of the formate ester.[122]

It is evident from Table IV that 2,5-dimethylphenyl acetate is rearranged by boron fluoride to 4-acetyl-2,5-dimethylphenol exclusively. A migration of a methyl group with the formation of 2-acetyl-4,6-dimethylphenol, as was observed by Auwers and co-workers in work with aluminum chloride as the catalyst,[123] does not take place. In the case of mesityl acetate-boron fluoride, with which a normal Fries rearrangement is impossible, no reaction takes place. Even after 45 hours of heating at its melting point, the mesityl acetate-boron fluoride complex is recovered unchanged[117]; on the other hand, aluminum chloride promotes the migration of a methyl group in mesityl acetate, which is followed by the rearrangement of the acetyl group, and 2,3,4-trimethyl-6-acetylphenol is obtained.[123]

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[121] I. G. Farbenindustrie A.-G., German Patent 637,808.

[122] Meerwein and Kästner, unpublished work.

[123] von Auwers, Bundesmann, and Wieners, *Ann.*, **447**, 164 (1926); von Auwers and Mauss, *Ber.*, **61**, 1500 (1928).

The Fries rearrangement not only occurs in the molten boron fluoride-ester complexes, but it also takes place in the crystalline solids. The boron fluoride complex of 2,4-dimethylphenyl acetate rearranges to 2-acetyl-4,6-dimethylphenol in 13 days at room temperature to the extent of 81.2%.

The investigation of the mechanism of the rearrangement has brought out new evidence which favors the idea originally suggested by Auwers and Mauss that the Fries rearrangement is an intramolecular reaction.[124] Other mechanisms have been proposed by Skraup and Poller[125] and by Rosenmund and Schnurr.[126] At first Rosenmund's data indicated that the rearrangement was an intermolecular reaction, in which the phenyl ester assumed the rôle of an acid anhydride in a Friedel-Crafts condensation, and thus effected the nuclear acylation of a second ester molecule. Although certain experimental facts tend to support each of these suggested mechanisms, as yet none of them has been definitely established.[127]

Phenyl acetate introduces an acetyl group into the nucleus of anisole quite easily in the presence of boron fluoride (Eq. 19). In a reaction carried out at 68°C. over a period of 45 minutes, *p*-methoxyacetophenone was produced in a yield of 75.5% along with a small amount of *p*-hydroxyacetophenone (14.4%). The nuclear acetylation of veratrole by phenyl acetate

$$C_6H_5OCOCH_3 + C_6H_5OCH_3 \xrightarrow{BF_3} CH_3COC_6H_4OCH_3 + C_6H_5OH \qquad (19)$$

is just as easy as that of anisole, but such is not the case with *o*-chloroanisole with which a much lower yield (14.1%) of the acetyl derivative was obtained. Phenyl acetate did not acetylate *o*-nitroanisole and toluene under similar conditions.

It is evident that in these reactions the phenol which is liberated undergoes nuclear acylation in the same way as does the phenol ether. The large yield of *p*-methoxyacetophenone can only be explained by the fact that contrary to expectation the acetylation of anisole proceeds more rapidly than that of phenol. It has also been shown that, when equimolecular quantities of anisole, phenol, and phenyl acetate are treated with boron fluoride under the same conditions used in the above experiments, 46.0% of *p*-hydroxyacetophenone and 44.7% of *p*-methoxyacetophenone were formed. The ratio of the rate of the nuclear acetylation of anisole by phenyl acetate in the presence of boron fluoride to that of phenol was calculated on the basis of the yields in the experiments with phenyl acetate and anisole alone and with phenol added to the mixture, and it was found to be 1.77. At the beginning of the reaction with phenyl acetate, phenol, and anisole, the nuclear substitution of phenol by the ester proceeded ten times as fast as the monomolecular rearrangement of phenyl acetate.

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[124] von Auwers and Mauss, *Ann.*, 464, 293 (1928); *Ber.*, 61, 1495 (1928); von Auwers, *ibid.*, 61, 416 (1928).

[125] Skraup and Poller, *Ber.*, 57, 2033 (1924).

[126] Rosenmund and Schnurr, *Ann.*, 460, 59 (1928).

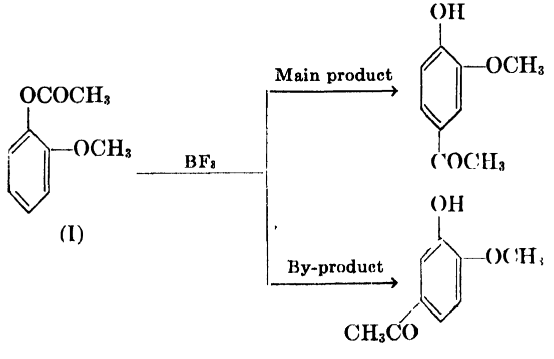
[127] For a discussion of the Fries reaction, see Blatt, *Chem. Revs.*, 27, 429 (1940); *Organic Reactions*, Wiley, New York, 1942, Vol. I, p. 342.

In explaining the mechanism for these reactions which aluminum chloride does not effect[124] there is the possibility that the real acetylating agent is not phenyl acetate but *p*-acetoxyacetophenone, $CH_3COC_6H_4OCOCH_3$, which results from the rearrangement and subsequent esterification of the phenyl acetate. In view of the relatively strong acidic properties of *p*-hydroxyacetophenone its ester can be looked upon to a certain extent as a mixed acid anhydride. As is expected from that, anisole is acetylated by *p*-acetoxyacetophenone in the presence of boron fluoride. The fact that the aryl esters themselves effect nuclear acetylation, however, could be proved also. When mesityl acetate, with which a similar reaction is out of the question, was used as the acetylating agent, *p*-methoxyacetophenone was formed in nearly a quantitative yield, although the reaction was very slow (steric hindrance). Phenyl acetate has been shown to effect the acetylation of phenols and phenol ethers in the presence of certain metal halides, but that does not necessarily indicate that it will acetylate a phenyl ester. If a mixture of phenyl acetate and 3,4-dihydrocoumarin, which is an intramolecular aryl ester and cannot be esterified further, is treated with boron fluoride in nitrobenzene under the same conditions under which phenyl acetate alone rearranges to the extent of 52.7%, the exclusive product is *p*-hydroxyacetophenone and it is formed in the same yield (56%). The nuclear acetylation of dihydrocoumarin by phenyl acetate does not take place.

Furthermore, the experiments which had led Auwers to the conclusion that the Fries rearrangement was an intramolecular reaction could be confirmed essentially. Auwers and Mauss[124] found that under certain conditions the Friedel-Crafts reaction with individual phenols led to products different from those obtained by the Fries rearrangement. The ether of 2,4-dimethylphenol reacted with acetyl chloride and aluminum chloride with the formation of 3-acetyl-4,6-dimethylphenol and its methyl ether as the main product. Only small quantities of the 2-acetyl derivative were isolated, the substance which is the only one obtained in the rearrangement of the acetate ester by aluminum chloride. The same products were obtained when the reaction was carried out under similar conditions but with the use of acetic acid or aryl acetates for acetylating agents and boron fluoride for the catalyst. Nevertheless, it was found that the ratio of the yields of the 2- and 3-acetyl derivatives was greater than that found in the reaction with aluminum chloride. Of the two acetylating agents the aryl acetate gave more of the 2-acetyl derivative than did acetic acid. This difference in behavior in so far as it is concerned with nuclear substitution exclusively is probably due to a difference in the $PZ°$ factor of the equation for the rate constant derived from the collision theory (the average number of collisions which result in reaction).

The reaction of 2,4-dimethylphenol with acetic acid in the presence of boron fluoride gave 48.5% of 2-acetyl-4,6-dimethylphenol and only 21.5% of the 3-acetyl derivative. *p*-Cresyl acetate, with which the Fries rearrangement takes place for the most part, reacted with 2,4-dimethylphenol methyl ether with the formation of about 14% of the 2-acetyl derivative and only small amounts of the 3-acetyl compound and its ether. Acetylation with mesityl acetate, with which a Fries rearrangement is impossible, produced 71.6% of the 2-acetyl derivative and only a trace (0.8%) of the ether of 3-acetyl-4,6-dimethylphenol.

In the case of the Fries rearrangement of the *O*-acyl compounds of monohydric phenols the acyl group always migrates to the ortho or para position, never to the meta. The rearrangements described in the literature in which the *O*-acyl group of polyhydric phenols and their ethers were found to have entered the meta position can be explained as nuclear acetylations rather than rearrangements. An example of such a reaction is that of guaiacol acetate (I) catalyzed by zinc chloride[128] and by boron fluoride,[117] in which the main product was *p*-acetylvanillone (II), and a small amount of the meta compound (isoacetovanillone) (III) was formed.



(II)

(III)

A determination of the kinetics of the Fries rearrangement of 0.2 molar solutions of boron fluoride-phenyl acetate in chlorobenzene, boron fluoride etherate, and nitrobenzene at 20°C. permitted no conclusions to be made as to whether the reaction is a mono- or bimolecular one. The reaction rate in these solvents falls off to such an extent that reasonably accurate constants for either type of reaction could not be calculated. Determination of the order of the reaction for the rearrangement of phenyl acetate in a mixture of 2 parts of boron fluoride-acetic acid (1:1) and 3 parts of nitrobenzene at 20° and at 30° gave reasonably good constants for a unimolecular reaction. At 20°C. the rate constant is 2.0×10^{-3}, and at 30° it is 5.5×10^{-3}. The temperature coefficient is therefore $K_{30}/K_{20} = 1.76$, which gives an activation energy of 18,000 cal. by substitution in the Arrhenius equation.

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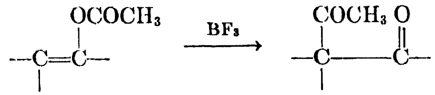
[128] Reichstein, *Helv. Chim. Acta*, 10, 392 (1927).

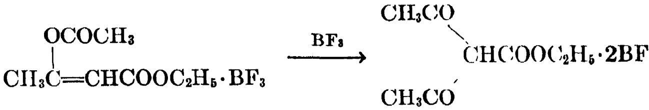
Boron fluoride-acetic acid does not act as a nuclear acetylating agent in these reactions. This was proved by the fact that in the case of 0.2 molar solutions of hydrocoumarin and 7-methylhydrocoumarin in the same solvent mixture used above no nuclear substitution took place in 20 hours at 20°C. In the same time and under the same conditions phenyl acetate was rearranged to the extent of 90%.

The rearrangement (Eq. 20) of enol acetates takes place under the influence of boron fluoride with the production of the *C*-acetyl compounds.[117]

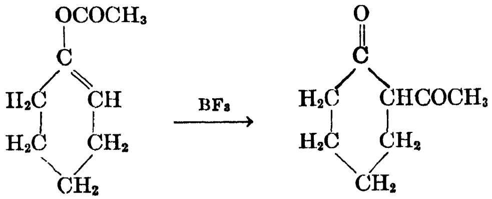


$$-\underset{|}{C}=\overset{\overset{\displaystyle OCOCH_3}{|}}{C}- \xrightarrow{BF_3} -\underset{|}{\overset{\overset{\displaystyle COCH_3}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}- \qquad (20)$$

In this way a *C*-acetyl acetoacetic ester was obtained (Eq. 21) very rapidly in a 93.5% yield from the *O*-acetyl derivative by the action of boron fluoride at low temperatures. Cyclohexenyl acetate (Eq. 22) rearranged a little less smoothly and produced 2-acetylcyclohexanone in about a 55% yield. These reactions also indicate that the Fries rearrangement is unimolecular.



$$CH_3\overset{\overset{\displaystyle OCOCH_3}{|}}{C}=CHCOOC_2H_5\cdot BF_3 \xrightarrow{BF_3} \begin{array}{l}CH_3CO\\ \qquad\diagdown\\ \qquad\; CHCOOC_2H_5\cdot 2BF_3\\ \qquad\diagup\\ CH_3CO\end{array} \qquad (21)$$

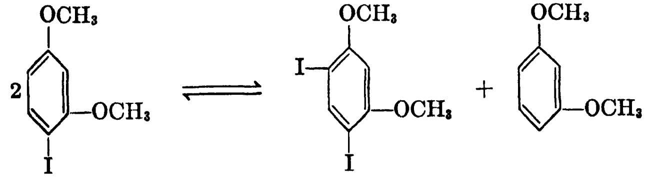


(22)

Since the phenyl esters were rearranged under mild conditions by boron fluoride, it was expected that the phenyl alkyl carbonates would rearrange to *o*- and *p*-hydroxybenzoic esters. Unfortunately, such a reaction did not take place; instead, in a reaction with phenyl ethyl carbonate carbon dioxide was eliminated, and *o*- and *p*-ethylphenols were isolated along with small quantities of 2,4-diethylphenol.[117]

C. Halogen Shifts in Aromatic Ethers

A peculiar rearrangement which was carried out originally by boron fluoride etherate is the exchange of halogen in 4-iodoresorcinol dimethyl ether (I) with the production of 4,6-diiodoresorcinol dimethyl ether (II), and resorcinol dimethyl ether (III).[129] Later it was found that this reaction was effected by other catalysts commonly used to promote isomerization reactions (such as ether solutions of stannic chloride, titanium tetrachloride, aluminum chloride, hydrochloric acid, sulfuric acid, etc.).

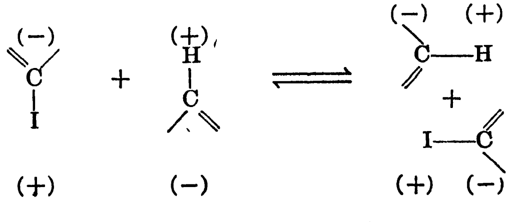


(I) (II) (III)

The reaction proceeds in a cold ether solution of boron fluoride etherate to the extent of 90%, since the diiodoresorcinol dimethyl ether is quite insoluble in ether and precipitates. The iodine exchange is an equilibrium reaction, since in reactions in which the diiodoresorcinol dimethyl ether remains in solution the rearrangement is incomplete. Further evidence that the reaction involves an equilibrium is furnished by the fact that when a hot mixture of 4,6-diiodoresorcinol dimethyl ether and resorcinol dimethyl ether is cooled quickly by pouring it on ice, a yield of 88% of 4-iodoresorcinol dimethyl ether can be isolated.

The iodine shift is an intermolecular reaction involving 2 molecules of 4-iodoresorcinol dimethyl ether, since in the rearrangement in ether solution by boron fluoride etherate no detectable quantities of free iodine are formed. Furthermore, resorcinol dimethyl ether is not iodinated by free iodine under the conditions of this reaction. On the other hand, boron fluoride catalyzes the iodination of anisole to the para and ortho (?) derivatives by the monoiodoresorcinol. The iodination of phenol produces *o*-iodophenol but the reaction proceeds less smoothly.

The catalyst increases the positive effect of the methoxyl group on the iodine atom in such a way that the iodine atom becomes rather loosely



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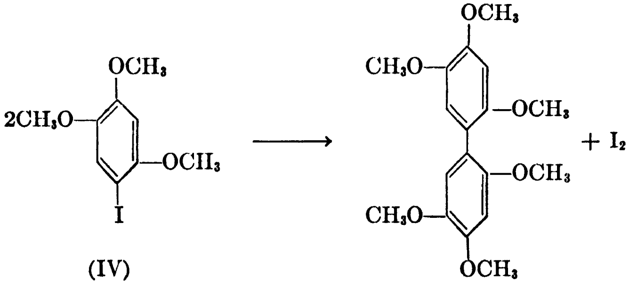
[129] Meerwein, P. Hofmann, and Schill, *J. prakt. Chem.*, **154**, 266 (1939).

attached and can displace a hydrogen atom from another molecule. The process is illustrated by the accompanying equilibrium scheme, which indicates that the halogen exchange occurs more readily the more strongly the halogen atom is polarized. The tendency for a halogen atom to shift must therefore decrease in the following order: iodides, bromides, chlorides, and fluorides.

The rearrangement of 4-bromoresorcinol dimethyl ether supports this conclusion, since it takes place with considerably more difficulty than the reaction with the iodo compound. The shift of bromine with the production of 4,6-dibromoresorcinol dimethyl ether does not occur in the presence of boron fluoride etherate alone, but it proceeds easily and produces the difficultly soluble dibromo ether in 55% yield when boron fluoride is introduced into a solution of the monobromo ether in boron fluoride etherate.

The reaction with the chloro compound is still more difficult. In this case a solution of 4-chlororesorcinol·dimethyl ether in boron fluoride etherate must be saturated with boron fluoride and heated for a long time in a sealed tube at 135°C. in order to effect the halogen shift. The product is the expected mixture of 4,6-dichlororesorcinol dimethyl ether and resorcinol dimethyl ether.

If the 6 position of 4-iodoresorcinol dimethyl ether is occupied by a methyl or better still a methoxyl group (IV), so that that position cannot be iodinated, the reaction leads to the coupling of 2 molecules and the precipitation of iodine in nearly a theoretical yield. A boron fluoride etherate solution of 5-iodohydroxyhydroquinone trimethyl ether at room temperature produces 2,2′,4,4′,5,5′-hexamethoxybiphenyl. This reaction also takes place at higher temperatures (reflux) without the use of catalysts. Anisole and resorcinol dimethyl ether cannot be iodinated by 5-iodohydroxyhydroquinone trimethyl ether whether a catalyst is present or not. Instead, iodine is precipitated in reactions involving them.



D. Decomposition of Diazonium Borofluorides

Another reaction of interest, which was the first useful one to lead to nearly quantitative yields of fluorobenzene,[130] is the decomposition of diazonium borofluorides. Benzenediazonium chloride is treated with fluoboric acid, which causes the precipitation of the slightly soluble benzenediazonium borofluoride. The dry crystalline diazonium salt has little tendency to explode at normal temperatures, but it decomposes as in Equation 23 upon being warmed. The boron fluoride liberated during the de-

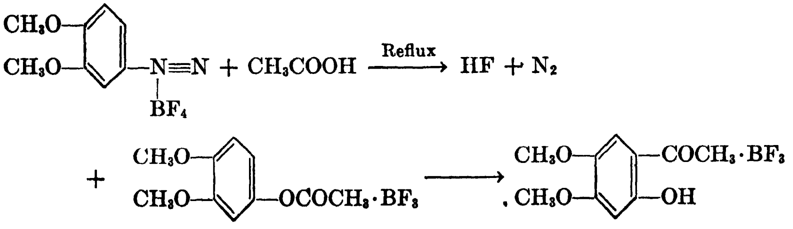
$$C_6H_5N_2BF_4 \longrightarrow C_6H_5F + N_2 + BF_3 \qquad (23)$$

composition can be re-used in other reactions. The method is applicable to the preparation of alkyl-, phenyl-, bromo-, and nitrofluorobenzenes, *o*-, *m*- and *p*-fluoroanisole, *p*-fluorodimethylaniline, and *p*-fluorobenzoic acid and its ethyl ester.[131] Other compounds which have been prepared in this way are α- and β-fluoronaphthalenes, *o*-, *m*-, and *p*-difluorobenzenes, 1,5-difluoronaphthalene, and 2,2′- 3,3′-, and 4,4′-difluorobiphenyls. The yields of the fluorinated compounds depend on the solubilities of the diazonium borofluorides in water and on their behavior on thermal decomposition. If they react very violently when they are warmed, as do the nitrobenzenediazonium borofluorides, it is expedient to modify the reaction by mixing an inert material (sand, sodium carbonate, alkali borofluoride) with the diazonium salt. It has been suggested that the diazonium borofluorides be decomposed *in vacuo*.[132]

The reaction of the dry diazonium borofluoride with acetic acid and acetic anhydride (Eq. 24) produces phenyl acetate.[133] This would seem to provide a method for preparing phenols which are otherwise accessible

$$C_6H_5N_2BF_4 + CH_3COOH \xrightarrow{\text{Reflux}} C_6H_5OCOCH_3{\cdot}BF_3 + HF + N_2 \qquad (24)$$

only in poor yields by refluxing aqueous solutions of their diazonium salts, which are often difficult to hydrolyze. Unfortunately the phenyl esters of such phenols obtained with difficulty by the other method undergo re-



(25)

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[130] Balz and Schiemann, *Ber.*, **60**, 1186 (1927). Schiemann, *J. prakt. Chem.*, **140** 97 (1934). Flood, in *Organic Syntheses*, Wiley, New York, 1943, Coll. Vol. II, p. 295.

[131] Schiemann and Winkelmüller, *Org. Syntheses*, **13**, 52 (1933); in *Organic Syntheses*, Wiley, New York, 1943, Coll. Vol. II, p. 299. See also Bockemüller, *Organisch Fluorverbindungen*, Enke, Stuttgart, 1936, p. 55; Edwards, Ann Arbor, 1945.

[132] Kleiderer and Adams, *J. Am. Chem. Soc.*, **53**, 1577 (1931).

[133] Haller and Schaffer, *J. Am. Chem. Soc.*. **55**, 4954 (1933).

arrangement very readily to the phenol ketones, and the reaction loses its significance. An example of such a rearrangement is the reaction (Eq. 25) of 3,4-dimethoxybenzenediazonium borofluoride in refluxing acetic acid; the ketone is formed immediately.[134]

3. Fischer Indole Synthesis

Boron fluoride has been found to be quite effective as a condensing agent for the conversion of phenylhydrazones to indole derivatives. With few exceptions the yields of indoles obtained by the use of boron fluoride are comparable to those obtained with other condensing agents.[135]

In the syntheses in which it is effective boron fluoride is a superior condensing agent because of the ease with which the products can be isolated and purified.

The phenylhydrazones form coordinate complexes with boron fluoride, which are decomposed most smoothly by heating them in the presence of solvents. The cyclization to indoles has been effected in the absence of solvents, but the reaction is so violent as to be somewhat explosive. The best solvent for the decomposition is acetic acid, but ethanol and benzene are useful in certain cases.

The boron fluoride, an excess of which should be avoided, is introduced into the reaction mixtures in several ways. It may be bubbled into a solution of the phenylhydrazone in an organic solvent, after which the mixture is heated to decompose the boron fluoride-phenylhydrazone complex. Another method consists of bubbling the gas through a refluxing solution of the phenylhydrazone in an organic solvent. The best method makes use of the fact that phenylhydrazones, being stronger bases than ether, displace ether from boron fluoride etherate. The addition of the boron fluoride as its etherate makes accurate measurement of the amount of catalyst possible.

The decompositions in solvents (acetic acid, ethanol, benzene) are carried out at the boiling point. Reaction mixtures in which acetic acid or benzene is used are worked up in one of two ways. In one the mixture is poured into water to dissolve the ammonia-boron fluoride and the product is extracted by ether; in the other, the ammonia-boron fluoride complex is filtered, and the product is crystallized from the hot filtrate.

In the absence of solvents, boron fluoride etherate is added to the phenylhydrazone and the boron fluoride complex formed is heated to about 100° to 130°C. After the vigorous reaction has ceased, the product can be isolated by an appropriate procedure.

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[134] L. E. Smith and Haller, *J. Am. Chem. Soc.*, 56, 237 (1934).

[135] Snyder and C. W. Smith, *J. Am. Chem. Soc.*, 65, 2452 (1943).

Formulas I to V illustrate a possible mechanism. The transitory colors observed during the synthesis are thought to be due to an equilib-

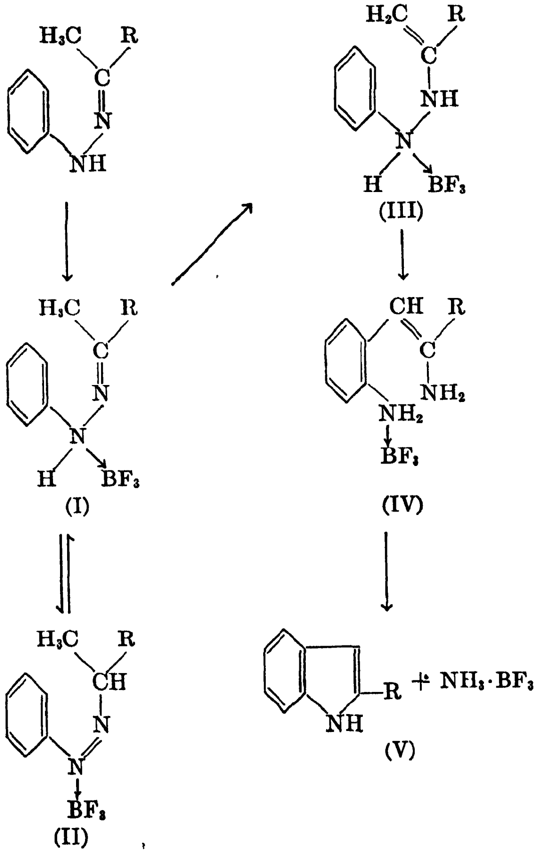


TABLE V

Reactions with Phenylhydrazones

Phenylhydrazone	Product	Yield, %	Other reagent	Yield, %
Methyl ethyl ketone	2,3-Dimethylindole	85*	$NiCl_2$	65
Isovaleraldehyde	3-Isopropylindole	60*	$ZnCl_2$	38
Acetophenone	2-Phenylindole	67.5†	$ZnCl_2$	80
Propiophenone	2-Phenyl-3-methylindole	87*	Cu_2Cl_2	72.5
Ethyl pyruvate	Indole-2-carboxylic acid	7.4‡	$ZnCl_2$	60
Cyclopentanone	Dihydropentindole	41*	H_2SO_4	45
Cyclohexanone	1,2,3,4-Tetrahydrocarbazole	93*	H_2SO_4	93

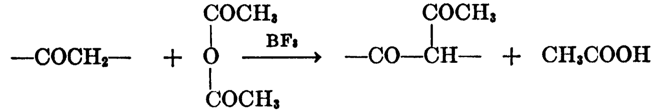
* The solvent was acetic acid.
† The solvent was benzene.
‡ No solvent was used.

rium between the colorless phenylhydrazone (I) and its colored phenylazo tautomer (II).

The phenylhydrazone of acetone would not undergo the reaction under the influence of boron fluoride; neither did the phenylhydrazone of acetaldehyde, which has not been condensed by any other agents. A few of the phenylhydrazones which have been used in the reaction and a comparison of the yields from their reactions with other condensing agents are given in Table V.

VI. SYNTHESES OF β-DIKETO COMPOUNDS. CONDENSATIONS INVOLVING REACTIVE HYDROGEN ATOMS

Boron fluoride can be used quite successfully for the catalysis of condensations between acid anhydrides and compounds containing the functional group, —CH_2CO—, a reaction which has not been carried out by the use of aluminum chloride and similar metal halides. The reaction is quite general and proceeds as in Equation 26.



$$\text{—COCH}_2\text{—} + \underset{\substack{|\\ \text{COCH}_3}}{\overset{\substack{\text{COCH}_3\\ |}}{\text{O}}} \xrightarrow{\text{BF}_3} \text{—CO—}\overset{\substack{\text{COCH}_3\\ |}}{\text{CH}}\text{—} + \text{CH}_3\text{COOH} \qquad (26)$$

Simply by saturating a cold mixture of a ketone (1 mole) and acetic anhydride (2 moles) by boron fluoride there is obtained a β-diketone.[70,114,136] The reaction between an ester and acetic anhydride yields β-keto esters,[117] and aliphatic acid anhydrides undergo a self-condensation with the production of anhydrides of β-keto acids.[70,114]

Condensations between acetic anhydride and the following ketones have been effected (the products are given in parentheses): acetophenone (benzoylacetone, 83%), tetralone (2-acetyltetralone), cyclohexanone (2-acetylcyclohexanone, 56%), diethyl ketone (β-acetyl diethyl ketone, 62.5%), and acetone (acetylacetone).

The acetylation of certain unsymmetrical aliphatic ketones by acetic anhydride showed that substitution took place on both sides of the keto group. The relative proportions of the two isomers in the case of ketones of the type, $CH_3COCH_2\overset{/}{\underset{\backslash}{C}}$—, appeared to be dependent on the number of hydrogen atoms on the β-carbon atom. The ratio of methylene to methyl substitution decreased as the number of β-hydrogen atoms decreased; thus, methyl ethyl ketone gave only the methylene derivative, methyl *n*-propyl ketone (also *n*-amyl and *n*-hexyl) afforded 90% of the methylene and 10% of the methyl derivative, and methyl isobutyl ketone yielded

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[136] Denoon, Jr., *Org. Syntheses*, 20, 6 (1940).

45% of the methylene and 55% of the methyl derivative. Attempts to acetylate methyl neopentyl ketone failed. The results obtained with these ketones are in contrast to those obtained by the acetylation of the same ketones by ethyl acetate in basic media, in which only the methyl derivatives were isolated.[137]

Extension of the reaction has been made recently to a number of higher aliphatic anhydrides including propionic, *n*-butyric, isobutyric, and *n*-caproic anhydrides.[138] Symmetrical and unsymmetrical aliphatic ketones, cyclohexanone, benzyl methyl ketone, and acetophenone were employed in studies to determine the usefulness of the reaction for synthetic purposes. The yields were generally in the region of 30 to 50%, with the ratios of the two derivatives possible in the case of the unsymmetrical ketones following the general rule mentioned in the previous paragraph. The reaction failed in attempted condensations involving phenylacetic anhydride and acetone and those with phthalic or succinic anhydride and acetophenone.

Unsaturated ketones have also been condensed with acetic anhydride, but these reactions did not proceed so smoothly because of the ready polymerization of the unsaturated ketones. The addition of hydrofluoric acid interfered still more with the desired reaction, since it increased considerably the tendency for polymerization. Even when boron fluoride which had been carefully purified to remove all traces of hydrofluoric acid was used for the condensation of benzalacetone and acetic anhydride (Eq. 27), only a 23% yield of ω-benzalacetylacetone was obtained. Mesityl oxide was polymerized so rapidly by boron fluoride that none of the β-diketone which was expected could be isolated.

$$C_6H_5CH{=}CHCOCH_3 + (CH_3CO)_2O \xrightarrow{BF_3} C_6H_5CH{=}CHCOCH_2COCH_3 + CH_3COOH \cdot BF_3 \qquad (27)$$

The reaction of acetic anhydride with an ester in the presence of boron fluoride was demonstrated in the case of 3,4-dihydrocoumarin with the production of a β-keto ester. In this reaction the hydrocoumarin was not only acetylated in the lactone ring but also underwent acetylation in the benzene nucleus. When boron fluoride was passed into a cooled solution of hydrocoumarin in acetic anhydride (in a molar ratio of 1:2), 3,6-diacetylhydrocoumarin was formed in a yield of 40.6%. The product (VI), which precipitated from the reaction mixture as a yellow solid, was an extremely stable chelate compound containing boron and fluorine. It may be regarded as a fluoborate ester of the enol form of the ketone. Removal of

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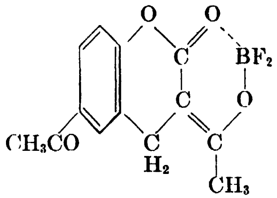
[137] Hauser and Adams, *J. Am. Chem. Soc.*, 66, 345 (1944).

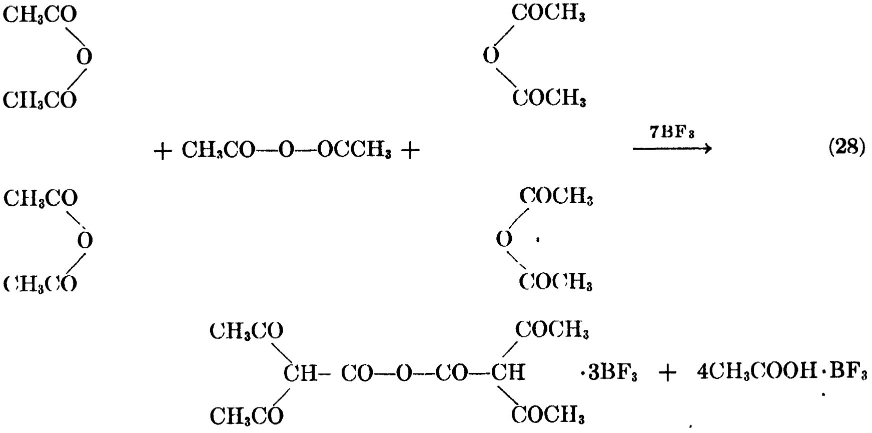
[138] Adams and Hauser, *J. Am. Chem. Soc.*, 67, 284 (1945).



(VI)

BF_2 from the chelate compound by melting it with crystalline sodium acetate converted it into 3,6-diacetylhydrocoumarin. The 3-acetyl group was removed by refluxing the compound with 2 *N* sodium hydroxide and 6-acetylhydrocoumarin was obtained.

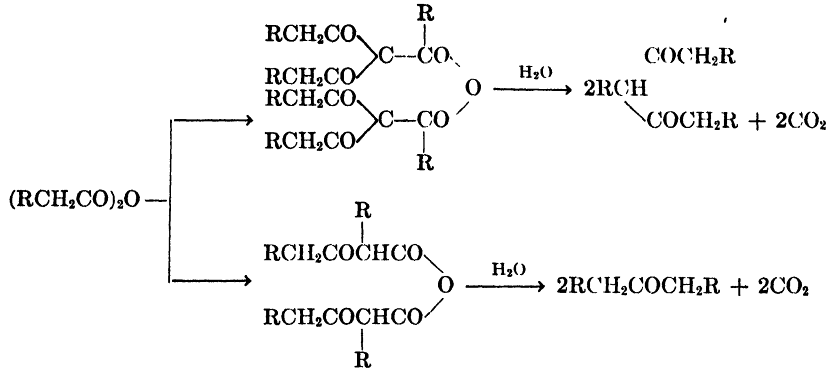
In reactions involving acetic anhydride, the self-condensation of the anhydride which was mentioned previously always occurs as a side reaction. An excellent yield (90.7%) of diacetylacetic acid can be obtained (Eq. 28) by saturating acetic anhydride, cooled in an ice-salt bath, by boron



(28)

fluoride (1.3 moles). The product crystallizes as the boron fluoride complex. Boron fluoride-monoacetic anhydride is not formed. Decomposition of the molecular compound with water gives 2 moles of acetylacetone and 2 moles of carbon dioxide.

In the case of the higher homologous fatty acid anhydrides, such as the anhydrides of propionic and butyric acids, formation of the monoacyl anhydride of the fatty acid is favored over production of the diacyl compound. Then the predominating product of the hydrolysis reaction is the monoketone, and only a small amount of a β-diketone is formed. The amounts of mono- and diketones obtained by this reaction are given in Table VI.



R = CH_3— or C_2H_5—

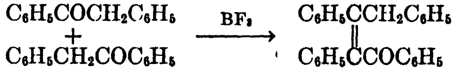
TABLE VI

Ketones from Condensation of Acid Anhydrides

Anhydride	Yield, %	
	Monoketone	Diketone
Acetic acid	0	90.6
Propionic acid	24.4	11.2
n-Butyric acid	66	6.2

The action of boron fluoride on the anhydride of isobutyric acid, which has only one hydrogen atom capable of substitution, produces the crystalline boron fluoride complex of the anhydride of isobutyrylisobutyric acid, $(CH_3)_2CH—CO—C(CH_3)_2CO—O—COC(CH_3)_2COCH(CH_3)_2 \cdot 3BF_3$. The decomposition of this product with water affords an 81.5% yield of diisopropyl ketone. In contrast to the results obtained with acetic and isobutyric anhydrides, no crystalline molecular complexes are precipitated when boron fluoride is passed into the anhydrides of propionic and butyric acids. The anhydrides of chloroacetic and phenylacetic acids give complex compounds with boron fluoride with which no self-condensation takes place. Thus the hydrolysis of the products merely regenerates the acids.

Not all ketones can be acetylated by acetic anhydride, as in some cases the reaction of the keto group with a reactive methylene group may take precedence over the other reaction. An example of this is the production of 1,2,3,4-tetraphenyl-2-buten-1-one from desoxybenzoin (Eq. 29).[114]



$$\begin{array}{c} C_6H_5COCH_2C_6H_5 \\ + \\ C_6H_5CH_2COC_6H_5 \end{array} \xrightarrow{BF_3} \begin{array}{c} C_6H_5CCH_2C_6H_5 \\ \| \\ C_6H_5CCOC_6H_5 \end{array} \qquad (29)$$

Breslow and Hauser[139] have extended the reaction to other compounds with reactive hydrogen atoms and have effected condensations which usually have been carried out in basic media. The method, which involved saturation of the reaction mixtures with boron fluoride, was very similar to those described previously for the production of β-diketones, β-keto esters, and anhydrides of β-keto acids.

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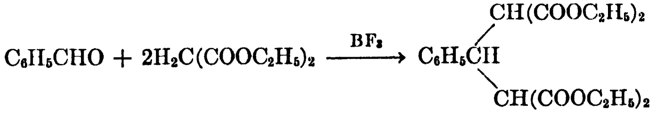
[139] Breslow and Hauser, *J. Am. Chem. Soc.*, 62, 2385 (1940).

The reaction between benzaldehyde and acetophenone (Eq. 30) af-

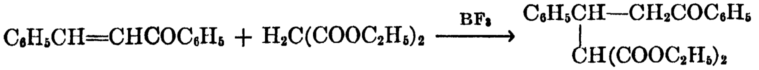
$$C_6H_5CHO + H_3CCOC_6H_5 \xrightarrow{BF_3} C_6H_5CH{=}CHCOC_6H_5 + H_2O \qquad (30)$$

forded a 61% yield of benzalacetophenone along with small quantities of benzaldiacetophenone. Benzaldehyde and diethyl malonate (Eq. 31) gave

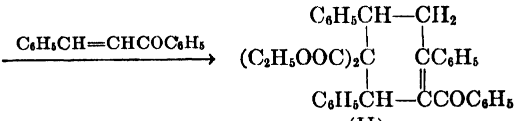


$$C_6H_5CHO + 2H_2C(COOC_2H_5)_2 \xrightarrow{BF_3} C_6H_5CH\begin{cases} CH(COOC_2H_5)_2 \\ CH(COOC_2H_5)_2 \end{cases} \qquad (31)$$

a 58% yield of 2-phenylpropane-1,1,3,3-tetracarboxylic acid tetraethyl ester. A similar reaction between benzalacetophenone and diethyl malonate formed 1-benzoyl-2-phenylpropane-3,3-dicarboxylic acid diethyl ester (I) and a little 1,3,5-triphenyl-2-benzoylcyclohexene-4,4-dicarboxylic acid diethyl ester (II) in a total yield of 13.3%.



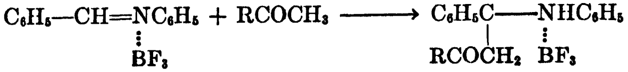
$$C_6H_5CH{=}CHCOC_6H_5 + H_2C(COOC_2H_5)_2 \xrightarrow{BF_3} \begin{array}{l} C_6H_5CH{-}CH_2COC_6H_5 \\ \vert \\ CH(COOC_2H_5)_2 \end{array} \qquad (I)$$



$$\xrightarrow{C_6H_5CH=CHCOC_6H_5} \begin{array}{ccc} & C_6H_5CH{-}CH_2 & \\ (C_2H_5OOC)_2C & & CC_6H_5 \\ & C_6H_5CH{-}CCOC_6H_5 & \end{array}$$

(II)

The addition to double bonds of compounds with reactive hydrogen atoms has been observed in reactions with benzalaniline. The following methyl ketones were added to benzalaniline-boron fluoride by Snyder, Kronberg, and Romig[140] (the yields of the β-amino ketones are given in parentheses): acetone (67%), ethyl methyl ketone (66%), isobutyl methyl ketone (61%), n-amyl methyl ketone (38%), 4-methylhexanone-2 (38%), benzylacetone (26%), acetophenone (62%), pinacolone (71%). Equation 32 illustrates the reaction.



$$\begin{array}{l} C_6H_5{-}CH{=}NC_6H_5 \\ \qquad\qquad\quad \vdots \\ \qquad\qquad\quad BF_3 \end{array} + RCOCH_3 \longrightarrow \begin{array}{l} C_6H_5C{-}{-}NHC_6H_5 \\ \quad\ \ \vert \qquad\ \vdots \\ RCOCH_2\ BF_3 \end{array} \qquad (32)$$

Of all the methyl ketones studied, acetomesitylene, mesityl oxide, and benzyl methyl ketone could not be made to react. Cyclopentanone condensed with benzalaniline-boron fluoride in 42% yield, but cyclohexanone added only to a slight extent and α-tetralone would not react under any conditions. Symmetrical ketones such as diethyl, di-*n*-butyl, and di-*n*-nonyl ketones as well as other compounds which would be expected to have reactive enough hydrogen atoms (benzyl cyanide, phenylacetylene, ethyl acetate, nitromethane, butyraldehyde) showed no tendency to react with the benzalaniline-boron fluoride complex.

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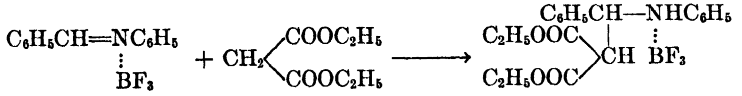
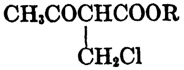
[140] Snyder, Kronberg, and Romig, *J. Am. Chem. Soc.*, **61**, 3556 (1939).

Ethyl malonate was the only compound of those having exceptionally reactive methylene groups which reacted with benzalaniline-boron fluoride without undergoing undesirable side reactions (Eq. 33). The yield, depending on the method, was 6%[140] or 26.5%.[141] Analogous addition products could not be isolated from reactions with acetoacetic ester,[140,141] cyanoacetic ester,[142] and dibenzoylmethane.[140]



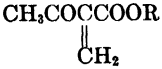
$$\underset{BF_3}{\underset{\vdots}{C_6H_5CH{=}NC_6H_5}} + CH_2\begin{cases}COOC_2H_5\\COOC_2H_5\end{cases} \longrightarrow \begin{matrix}C_2H_5OOC\\C_2H_5OOC\end{matrix}\!\!>\!CH{-}\overset{}{CH(C_6H_5)}{-}\underset{BF_3}{\underset{\vdots}{NHC_6H_5}} \qquad (33)$$

On the other hand, acetoacetic ester was alkylated by benzyl alcohol in the presence of boron fluoride with the production of 20.4% of *C*-benzylacetoacetic ester.[139] *C*-Isopropylacetoacetic ester was obtained in alkylations with isopropyl alcohol (40.4%),[140] diisopropyl ether (70.9%),[140] and isopropyl acetate.[142] Ethyl acetoacetate has also been alkylated by cyclohexanol (34%), *tert*-butyl alcohol, ethyl *tert*-butyl ether, and dibenzyl ether (18%) with the production of the corresponding α-alkyl derivatives.[142] Side reactions which interfered with the reaction were the dehydration of the alcohols and polymerization of the olefins formed and ester interchange between the ethyl acetoacetate or the alkylated product and the alcohol. The failure of other alcohols to effect alkylations was thought to be due to predominating side reactions. Boron fluoride appeared to form a crystalline complex with ethyl benzoyl acetate, and as a result attempted alkylations of the ester failed. The mechanism of alkylation with alcohols has been discussed previously in the section dealing with the alkylation of aromatic hydrocarbons. Data on the acylation of ketones with anhydrides indicates that the enol form of the compound is acylated, but it is not known whether enolization is a prerequisite to alkylation. Recently



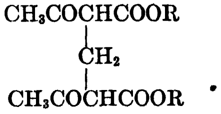
$$CH_3CO\underset{CH_2Cl}{\underset{|}{C}}HCOOR$$

(III)



$$CH_3CO\underset{CH_2}{\underset{\|}{C}}COOR$$

(IV)



$$CH_3CO\underset{CH_3CO\overset{|}{C}HCOOR}{\underset{CH_2}{\underset{|}{C}}}HCOOR$$

(V)

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[141] Hauser and Breslow, *J. Am. Chem. Soc.*, 62, 2389 (1940).

[142] Breslow and Hauser, *J. Am. Chem. Soc.*, 62, 2611 (1940); Hauser and Adams, *ibid.*, 64, 728 (1942); Adams, Abramovitch, and Hauser, *ibid.*, 65, 552 (1943).

the alkylation of acetoacetic ester by chloromethyl ether has been investigated.[143] The product, methylenediacetoacetic ester (V), was obtained in 33% yield along with a certain amount of a non-distillable residue. The reaction is believed to involve chloromethylation of the keto ester as the initial step. This intermediate (III) then alkylates another mole of acetoacetic ester directly or does so by another type of reaction involving the loss of hydrogen chloride, which produces IV. The methylene acetoacetic ester (IV) then alkylates another mole of acetoacetic ester by means of a Michael condensation or possibly by a boron fluoride-catalyzed olefin alkylation reaction.

An attempt to use boron fluoride in the Perkin reaction was succesful, but only a 4.5% yield of cinnamic acid could be isolated. The condensation was carried out by saturating a mixture of benzaldehyde and acetic acid with boron fluoride at 0°C.

Boron fluoride has also been used to catalyze the condensations of the carbonyl group with formic esters and with aromatic compounds (Eq. 34).

$$\mathrm{HCHO + HCOOR \xrightarrow{BF_3} HOCH_2COOR} \tag{34}$$

From the reactions between paraformaldehyde and alkyl formates were isolated alkyl esters of glycolic acid,[144] and the condensation (Eq. 35) between anisole and acetic acid in the presence of boron fluoride produced *p*-methoxyacetophenone and a small amount of 1,1,1-tri-*p*-anisylethane.[117]

$$\begin{gathered}\mathrm{CH_3OC_6H_5 + CH_3COOH \xrightarrow{BF_3} CH_3OC_6H_4COCH_3 + H_2O} \\ \mathrm{CH_3OC_6H_4COCH_3 + 2C_6H_5OCH_3 \xrightarrow{BF_3} (CH_3OC_6H_4)_3CCH_3 + H_2O}\end{gathered} \tag{35}$$

VII. CLEAVAGE OF ETHERS

The cleavage of aliphatic ethers by acid chlorides or anhydrides takes place rather easily in the presence of anhydrous metal chlorides (such as ferric chloride, aluminum chloride, or zinc chloride). The products of the reaction, depending on the reagent used for the cleavage, are 1 mole each of an alkyl halide and an ester (Eq. 36) or 2 moles of an ester (Eq. 37).[145] Boron fluoride has been used successfully as a catalyst for this reaction and its use has been of value in determining the mechanism of the cleavage.[146]

$$\mathrm{ROR + R'COCl \xrightarrow{MeCl_n} RCl + R'COOR} \tag{36}$$

$$\mathrm{ROR + (R'CO)_2O \xrightarrow{MeCl_n} 2R'COOR} \tag{37}$$

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[143] Levine and Hauser, *J. Am. Chem. Soc.*, **67**, 2050 (1945).
[144] E. I. du Pont de Nemours and Co., U. S. Patent 2,211,693.
[145] Knoevenagel, *Ann.*, **302**, 133 (1914).
[146] Meerwein and Maier-Hüser, *J. prakt. Chem.*, **134**, 51 (1932).

The cleavage of ethers with acid chlorides does not proceed as well with boron fluoride as it does in the presence of the metal chlorides usually employed for such a reaction ($ZnCl_2$, $SnCl_4$, $ZnCl_4$, $TiCl_4$, $FeCl_3$, $AlCl_3$, $SbCl_3$). Only traces of ethyl benzoate could be detected after heating benzoyl chloride and ethyl ether at 110°C. for 6 hours with boron fluoride. The reaction progressed more successfully when the benzoyl chloride was replaced by acetyl chloride; in that case the cleavage of the ether took place more rapidly under the same conditions and ethyl acetate and ethyl chloride were isolated in a yield of 68.1%.

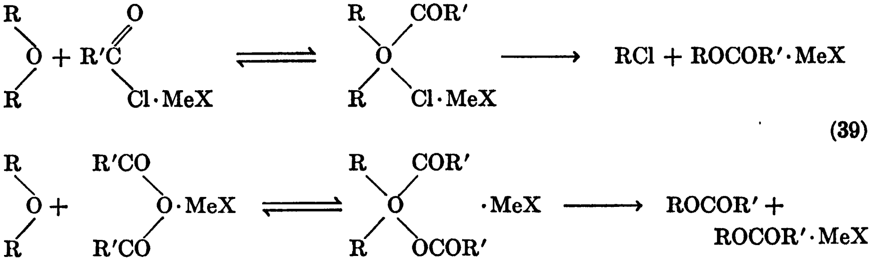
The reaction with acid chlorides can be effected more easily than the cleavage of ethers with acid anhydrides when the metal chlorides are used for catalysts. The reaction in the latter case is complicated by the fact that metal (or non-metal) halides react with acid anhydrides. For example, boron trichloride and acetic anhydride react readily at low temperatures with the formation of acetyl chloride and the tetraacetate of pyroboric acid (Eq. 38). This reaction does not take place with boron fluoride,

$$5(CH_3CO)_2O + 2BCl_3 \longrightarrow 6CH_3COCl + (CH_3COO)_2B{-}O{-}B(OCOCH_3)_2 \quad (38)$$

and the cleavage of ethers with it is more successful when anhydrides rather than acid chlorides are used. Although ethyl ether was cleaved by acetic anhydride and boron fluoride at 100°C. with the formation of a 59.1% yield of ethyl acetate, acetyl chloride under the same conditions gave only a 22.7% yield of the ester. High temperatures are unnecessary, as the reaction has been effected at room temperature when acetic anhydride was used; after 15 hours a 14.8% yield of ethyl acetate was obtained from equivalent quantities of ether, boron fluoride, and acetic anhydride, and after 16.5 months the yield was 71.6%. Succinic anhydride did not react with ether as readily as did acetic anhydride, and only at higher temperatures could the cleavage of ether by it be carried out in the presence of boron fluoride. The yields of diethyl succinate were 58% at 150° and 74.7% at 200°. The reaction with phthalic anhydride was still more difficult, and could be effected only at 200°.

It is assumed that the first step in the cleavage reaction is the addition of the acid chloride or anhydride in the form of its molecular compound with the metal (or non-metal) halide to a molecule of ether. The resulting complex is a tertiary oxonium salt, the formation of which is made possible by the fact that the complex formed between the anhydride or acid chloride and the halide increases the acidity of the acid from which the anhydride or chloride is derived. That such ternary molecular compounds are capable of existence has been proved in the case of dimethylpyrone, which gives crystalline complex compounds with acetyl chloride and with antimony pentachloride. The preparation of tertiary oxonium salts, which will be described later, is further evidence for the probable existence of the molecular compounds postulated as intermediates in this reaction.

The oxonium salt formed in the initial step has a tendency to dissociate into components different from those from which it was formed, and it is cleaved in that direction. Equations 39 illustrate this reaction.

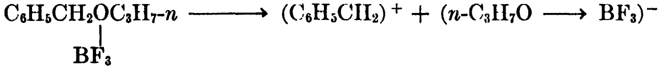


(39)

It is thought that the metal halide complex of the acid chloride (or anhydride) rather than the ether-metal halide complex initiates these reactions. The cleavage of diethyl ether by acetic anhydride in the presence of boron fluoride has been carried out both in excess ether and in excess acetic anhydride under conditions which were otherwise the same. In the case in which excess ether was used (5 moles of ether to 1 mole each of acetic anhydride and boron fluoride), the boron fluoride was attached primarily to the ether molecules by complex formation, and only traces of ethyl acetate were isolated. In the other case (2 moles of acetic anhydride to 1 each of ether and boron fluoride) a 71% yield of ethyl acetate was obtained. There is no doubt therefore that the molecular complexes of the halides with the anhydride or acid chloride effect the cleavage reaction. The easier cleavage of ethers by anhydrides than with acid chlorides in the presence of boron fluoride, the less successful reactions with succinic and phthalic anhydrides than with acetic anhydride, and the superiority of acetyl chloride over benzoyl chloride are all explainable on the basis that the tendency for a cleavage reaction to take place depends on the tendency for boron fluoride to form a coordinate complex with the reagent used in the reaction.

The cleavage of ethers by anhydrides or by acid chlorides may be carried out either with catalytic or with molar quantities of metal or non-metal halides, depending on the stability of the metal halide complex of the ester formed as contrasted to that of the coordinate complex with the reagent used for the cleavage reaction. If the molecular compound of the anhydride or acid chloride is more stable than that of the ester formed, it is continually re-formed during the course of the reaction by removal of the halide from the ester by anhydride or acid chloride which has not reacted; thus, catalytic quantities of the catalyst are sufficient to effect the cleavage. In the other case, in which the ester complex is more stable, the catalyst is removed permanently from the reaction mixture and molar quantities of it are necessary. The reaction of ether with acetic anhydride is an example of the first type of reaction, because only catalytic quantities of boron fluoride are necessary, while the cleavage by acetyl chloride, which requires molar quantities of boron fluoride, is an example of the second type.

Evidence obtained by Monacelli and Hennion in the cleavage of benzyl *n*-propyl ether by boron fluoride in solution in acetic acid, acetic anhydride, benzene, naphthalene, and phenol led them to the conclusion that the compound splits (Eq. 40) with the formation of a benzyl cation and a



$$\underset{\displaystyle BF_3}{C_6H_5CH_2\underset{|}{O}C_3H_7\text{-}n} \longrightarrow (C_6H_5CH_2)^+ + (n\text{-}C_3H_7O \longrightarrow BF_3)^- \qquad (40)$$

propoxy-boron fluoride anion.[147] In decompositions in acetic acid or anhydride considerable *n*-propyl acetate but no benzyl acetate was formed The benzyl fragment was converted to a polybenzyl polymer which gave anthracene on pyrolysis.

On the other hand, when the reaction was effected in the presence of aromatic compounds (benzene, naphthalene, phenol), the corresponding mono- and polybenzyl-substituted compounds were isolated. The propoxy group was thought to be converted to *n*-propyl alcohol. The alkylated products were formed exclusively when 0.5 mole of boron fluoride per mole of ether was employed, but by increasing the quantity of boron fluoride used in reactions in benzene, the alcohol formed could be used up to some extent in alkylating the benzene. The authors have also suggested that a cationic intermediate occurs in the formation of the isopropylbenzene, in which the *n*-propyl ion rearranges (Eq. 41) to the iso form before reacting.

$$n\text{-}C_3H_7OH\cdot BF_3 \longrightarrow (i\text{-}C_3H_7)^+ + (HO\cdot BF_3)^- \qquad (41)$$

Conclusive evidence that the two fragments of the cleavage of benzyl *n*-propyl ether reacted in different ways was obtained by effecting the decomposition in an acetic acid-benzene mixture. The products were *n*-propyl acetate and diphenylmethane, as was expected from the observations made previously with each solvent alone.

Aliphatic acids as well as their derivatives can effect the cleavage of ethers at elevated temperatures in the presence of boron fluoride.[109] Ethyl propionate was formed in a yield of 54% in 3 hours by the reaction between ether (2 moles), propionic acid (1 mole), and boron fluoride ($^1/_3$ mole) at 200 °C. No better yields of the ester were obtained by increasing the

$$C_2H_5OC_2H_5 + 2C_2H_5COOH \xrightarrow{BF_3} 2C_2H_5COOC_2H_5 + H_2O \qquad (42)$$

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[147] Monacelli and Hennion, *J. Am. Chem. Soc.*, **63**, 1722 (1941).

quantity of the catalyst. Other reactions of this type which have been carried out are the following (the products and yields are in parentheses): acetic acid and diethyl ether (ethyl acetate, 47%), cinnamic acid and diethyl ether (ethyl cinnamate, 43%), acetic acid and di-*n*-butyl ether (*n*-butyl acetate, 40%), propionic acid and diisoamyl ether (isoamyl propionate, 32%), and benzoic acid and diisoamyl ether (isoamyl benzoate, 21%).

The reactions of the ethylene oxides in the presence of boron fluoride are included here, since they involve cleavage of one of the carbon-oxygen linkages, although the behavior of these cyclic ethers is not entirely analogous to the normal ethers. When ethylene oxides are heated with boron fluoride alone, polymers are formed, and even when reactive substances are present in the reaction mixtures polymerization always takes place as a side reaction.

In reactions with alcohols the oxide ring is opened with the formation of good yields (60 to 75%) of the monoethers of the ethylene glycols. Cyclic oxides which have been used in this reaction are ethylene oxide, epichlorohydrin, pseudobutylene oxide, isobutylene oxide, 3-methoxypropylene oxide, and cyclohexene oxide. Ketones and aldehydes reacted with these oxides with the production of cyclic acetals, the yields of which varied from 20 to 50%, depending on the particular compounds involved. Ethylene oxide reacted with acetone and methyl propyl ketone with the formation of 2-methyl-2-ethyldioxolane (19%) and 2-methyl-2-propyldioxolane (21.5%), respectively. The yields obtained with 3-methoxypropylene oxide and with pseudobutylene oxide wére somewhat better (30 to 40%).[93]

Acids reacted normally, but acid chlorides caused the polymerization of the oxides to take place exclusively.

VIII. TERTIARY OXONIUM SALTS

By means of the action of acid anhydrides on ethylene oxides esters of the corresponding glycols are obtained very easily. Since the reactivity of the boron fluoride etherates toward anhydrides is comparable to that of the ethylene oxides, the reaction between boron fluoride etherate and ethylene oxide was studied.[148]

When boron fluoride etherate was added dropwise to epichlorohydrin, the reaction mixture became quite warm and before long a colorless crystalline compound precipitated. The addition of water to the reaction mixture gave a 72% yield of γ-chloropropylene glycol α-monoethyl ether ($ClCH_2$-$CHOHCH_2OC_2H_5$) along with large quantities of ethanol. Investigation of the crystalline and liquid components of the products of the reaction showed that the crystalline solid was triethyloxonium borofluoride, $(C_2H_5)_3$-OBF_4, and the ether solution contained primarily the neutral borate of γ-chloropropylene glycol monoethyl ether (I). Small quantities (10%) of

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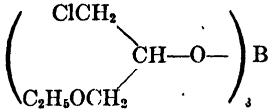
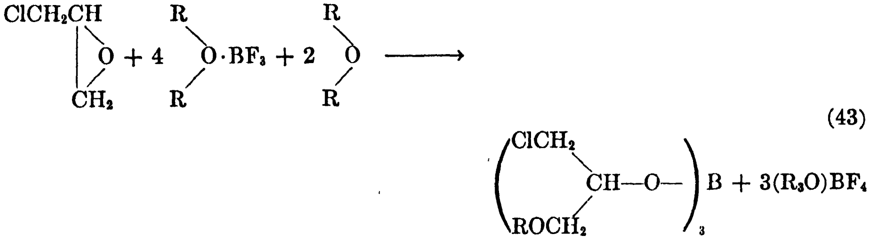
[148] Meerwein, Hinz, P. Hofmann, Kroning, and Pfeil, *J. prakt. Chem.*, **147**, 257 (1937).



(I)

the boron fluoride complex with γ-chloropropylene glycol monoethyl ether were also isolated.

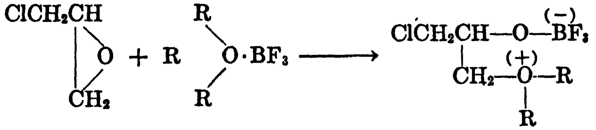
The complete reaction between boron fluoride etherate and the ethylene oxides, especially with epichlorohydrin in excess ether, can be written as in Equation 43. In the case of boron fluoride-dimethyl ether the reaction takes place at −35°C. (yield of oxonium salt, 98.2%), while with boron fluoride-diethyl ether it is necessary to effect the reaction at the boiling point of ether. Only a 30% yield of the oxonium salt of di-*n*-propyl ether is obtainable,[149] and higher ethers do not form oxonium salts. In an analogous way oxonium salts can be prepared with antimony pentachloride, ferric chloride, and aluminum chloride.



(43)

$R = CH_3—, C_2H_5—, n\text{-}C_3H_7—$

Evidence for the individual steps of the reaction which lead to the formation of the tertiary oxonium salts could be obtained by the isolation of intermediate compounds and by comparisons with analogous reactions. The first product from the action of boron fluoride on epichlorohydrin at low temperatures is an inner tertiary oxonium salt (II). This betaine-like salt which is formed contains a molecule of ether of crystallization tied



(II)

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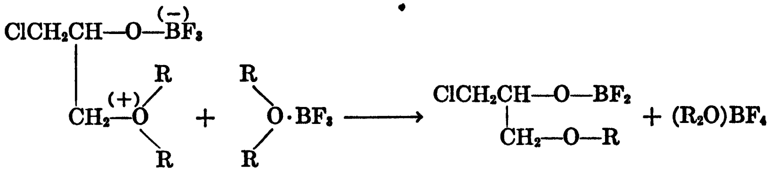
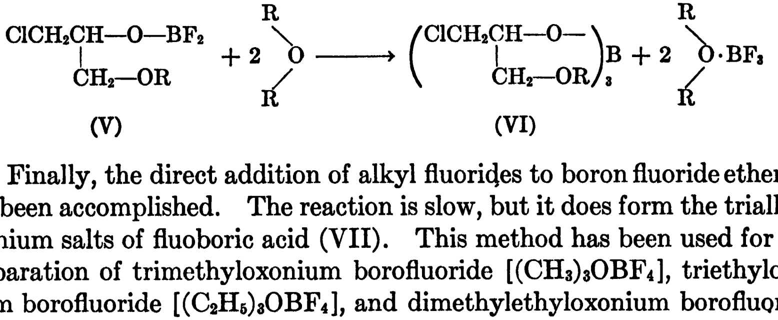
[149] Meerwein, Battenberg, Gold, Pfeil, and Willfang, *J. prakt. Chem.*, **154**, 83 (1939).

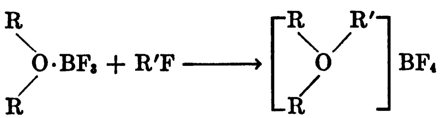
in with the boron fluoride compound. It reacts with more boron fluoride etherate (III), as could be shown *in vitro,* with the formation of the tertiary oxonium salt (IV). There is no doubt that the rapid and


(II) (III) (V) (IV)

quantitative formation of the trialkyloxonium borofluoride in this step is spontaneous, and that it proceeds by the addition of an alkyl fluoride in the form of the ions R^+ and F^- which are produced by the cleavage of the heteropolar inner oxonium salt. The difluoborate ester of the γ-chloropropylene glycol monoalkyl ether (V) formed along with the oxonium salt does not seem to be stable, but it disproportionates immediately in the presence of ether with the production of the borate of γ-chloropropylene glycol monoethyl ether (VI).


(V) (VI)

Finally, the direct addition of alkyl fluorides to boron fluoride etherate has been accomplished. The reaction is slow, but it does form the trialkyloxonium salts of fluoboric acid (VII). This method has been used for the preparation of trimethyloxonium borofluoride [$(CH_3)_3OBF_4$], triethyloxonium borofluoride [$(C_2H_5)_3OBF_4$], and dimethylethyloxonium borofluoride [$(CH_3)_2OC_2H_5BF_4$].

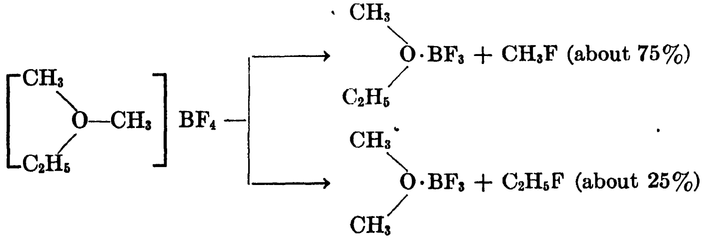

(VII)

The tertiary oxonium salts are decidedly salt-like in character, proof of which was obtained by conductivity measurements in liquid sulfur dioxide. They dissolve in liquid sulfur dioxide, nitrobenzene, nitromethane, methylene chloride, and acetone, but they are insoluble in other organic solvents.

The thermal decomposition of the oxonium salts produces boron fluoride etherate and alkyl fluorides (Eq. 44). Oxonium salts containing dif-

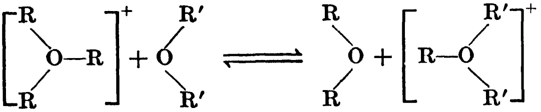
$$[(C_2H_5)_3O]BF_4 \longrightarrow (C_2H_5)_2O\cdot BF_3 + C_2H_5F \qquad (44)$$

ferent alkyl groups decompose in all possible ways, but in the case of dimethylethyloxonium borofluoride the decomposition forms primarily fluoromethane and boron fluoride-methyl ethyl ether (Eq. 45).



(45)

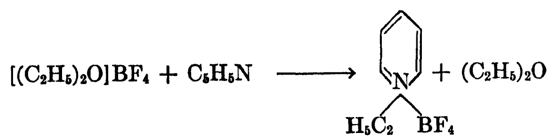
The trialkyloxonium salts are exceptionally reactive substances. The removal of one of their alkyl groups as a positive ion (which reacts with another molecule or anion) is very easy. Thus alkyl ions of the salt shift to ether molecules with different alkyl groups, in so far as the steric structure of the ether permits, until an equilibrium is reached.



(46)

The reaction between triethyloxonium borofluoride and dimethyl ether produces the difficultly soluble trimethyloxonium borofluoride at room temperature. In 5 days the reaction is practically quantitative, since the precipitation of the trimethyl salt displaces the equilibrium in its favor. Removal of the ether which is liberated during the process also displaces the equilibrium and causes the reaction to go to completion.

Not only oxygen-containing bases but also sulfur and nitrogenous bases react with oxonium salts. Triethyloxonium borofluoride reacts with pyridine with the production of fluoboric acid and *N*-ethylpyridine (Eq. 47).



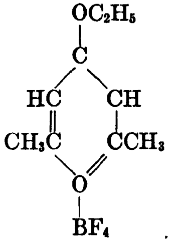
(47)

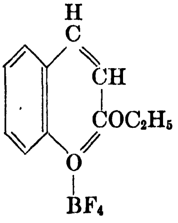
In the same way a mixture of mono-, di-, and trialkylamines and quaternary ammonium salts is obtained by the reaction between ammonia and an oxonium salt at low temperatures. Secondary and tertiary amines are formed predominantly when slightly more than 1 mole of ammonia is used for each mole of oxonium salt.

Triethylsulfonium borofluoride is obtained practically quantitatively by the reaction between diethyl sulfide and triethyloxonium borofluoride.

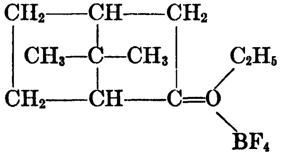
$$[(C_2H_5)_3O]BF_4 + (C_2H_5)_2S \longrightarrow [(C_2H_5)_3S]BF_4 + (C_2H_5)_2O \qquad (48)$$

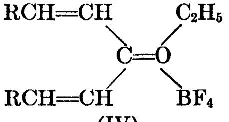
Dimethylpyrone and coumarin also react readily with the triethyloxonium salt with the production of ethoxypyrylium (I) or benzopyrylium (II) salts.


(I)


(II)

Addition products are formed by ketones with the oxonium salts. The addition compounds of the saturated ketones are colorless; therefore the product of the addition of triethyloxonium borofluoride must have the formula shown by III. Those of the unsaturated ketones are intensely colored. Whether they have an oxonium (IV) or a carbonium (V) salt structure has not yet been established.


(III)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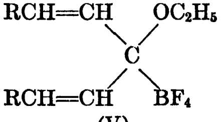
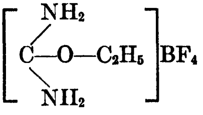

(V)

Other compounds which react with oxonium salts exceptionally easily at room temperature are acid amides, sulfoxides, and amines. Urea gives the fluoborate of *O*-ethylisourea (VI), and acetamide yields the fluoborate of acetimino ether (VII), when reactions with triethyloxonium borofluoride are carried out. With diethyl sulfoxide is obtained the diethylhydroxy-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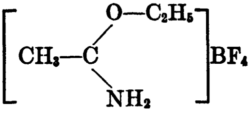
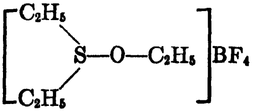
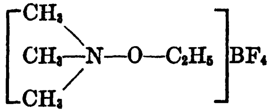

(VII)

sulfonium salt (VIII), and with trimethylamine oxide, the trimethylhydroxyethylammonium salt (IX).


(VIII)


(IX)

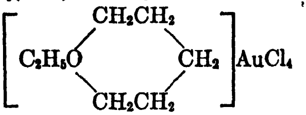
Since the cleavage of an alkyl group from a tertiary oxonium salt by the action of various reagents is very easy, the salts have been employed for the alkylation of water, alcohols, phenols, and acids. The reaction with water results exclusively in the formation of an aclohol as in Equation 49. The fact that the hydrolysis of an oxonium salt in aqueous solutions

$$[R_3O]BF_4 + H_2O \longrightarrow R_2O + ROH + HBF_4 \qquad (49)$$

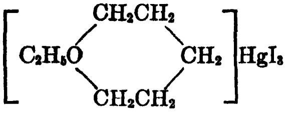
does not take place instantaneously permits the measurement of the velocity of the reaction by the determination of the conductivity of the solution. It was found that the rates of hydrolysis of different oxonium salts varied widely. Triethyloxonium borofluoride was found to be considerably more stable to water than the trimethyl salt, a fact which is in agreement with the greater tendency for the cleavage of fluoromethane rather than ethyl fluoride when dimethylethyloxonium borofluoride undergoes thermal decomposition.

The slow hydrolysis of the oxonium salts in aqueous solution also permits the production of the difficultly soluble oxonium salts of other acids by double decomposition reactions. In this way the following tertiary oxonium salts have been prepared:

$[(CH_3)_3O]AuCl_4$
$[(C_2H_5)_3O]AuCl_4$
$[(CH_3)_2OC_2H_5]AuCl_4$



$[(C_2H_5)_3O]_2SnCl_6$
$[(CH_3)_3O]HgI_3$
$[(C_2H_5)_3O]HgI_3$



$[(CH_3)_3O]_2PtCl_6$
$[(C_2H_5)_3O]_2PtCl_6$
$[(CH_3)_3O]SbCl_6$
$[(C_2H_5)_3O]SbCl_6$
$[(CH_3)_3O]Bi_2I_7$
$[(C_2H_5)_3O]Bi_2I_7$
$[(C_2H_5)_3O]Bi_2Cl_7$
$[(C_2H_5)_3O]_2H_2[Fe(CN)_6] + 2H_2O$
$[(C_2H_5)_3O]O \cdot C_6H_2(NO_2)_3$

These salts vary to a great extent in their stabilities, the most stable being those containing antimony and gold, which keep well for long periods of time in the absence of moisture. The least stable salts are those of bismuth and cadmium, which are so unstable that the isolation of pure samples of them was extremely difficult. The mercury, platinum, and tin salts fall between these two extremes.

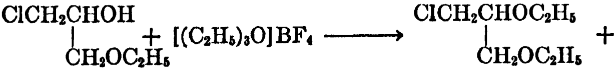
If triethyloxonium borofluoride is allowed to act on aqueous solutions of halogen or pseudohalogen salts, not only alkylation of the hydroxyl ion from the water but also that of other anions takes place. The tendency for alkylation of the halogen ions varies with their polarizability. Therefore both reactions 50 and 51 take place simultaneously. By the reactions

$$R_3O^+ + OH^- \longrightarrow R_2O + ROH \qquad (50)$$

$$R_3O^+ + An^- \longrightarrow R_2O + RAn \qquad (51)$$

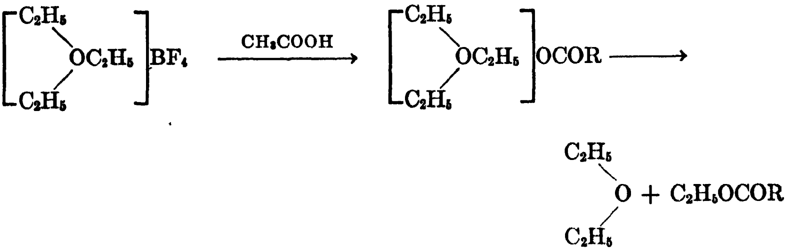
of this borofluoride with 2 N solutions of sodium fluoride, chloride, bromide, iodide, thiocyanate, and cyanide the following yields of alkylation products were obtained: ethyl fluoride (traces), chloride (12%), bromide (23%), iodide (53%), thiocyanate (64%), cyanide (55%). The yield of sodium cyanide was somewhat lower than that from the thiocyanate because of the extensive hydrolysis of sodium cyanide in aqueous solutions. The higher concentration of the hydroxyl ion increases the extent to which Reaction 50 is involved.

The alkylation of alcohols and phenols leads to the production of the corresponding ethers. The reaction (Eq. 52) between γ-chloropropylene glycol monoethyl ether and triethyloxonium borofluoride produced a 55% yield of γ-chloropropylene glycol diethyl ether, the preparation of which is extremely difficult by other methods. Phenetole was obtained in a 73% yield from phenol and the same oxonium salt, and the use of aqueous sodium phenolate raised the yield to 91%.



$$\begin{matrix}ClCH_2CHOH\\ |\\ CH_2OC_2H_5\end{matrix} + [(C_2H_5)_3O]BF_4 \longrightarrow \begin{matrix}ClCH_2CHOC_2H_5\\ |\\ CH_2OC_2H_5\end{matrix} + (C_2H_5)_2O + HBF_4 \qquad (52)$$

Esters are formed in the reactions between acids and tertiary oxonium salts. A 46% yield of ethyl acetate has been obtained (Eq. 53) from ace-



(53)

tic acid and triethyloxonium borofluoride. Better yields resulted from the use of aqueous solutions of the alkali salts of the acids. The reaction between the above oxonium salt and sodium benzoate gave a 71% yield of ethyl benzoate, and sodium 3,5-dinitrobenzoate afforded a mixture of 70% of the methyl ester and 30% of the ethyl ester in a reaction with dimethylethyloxonium borofluoride. This reaction confirms the evidence mentioned previously that the cleavage of a methyl group occurs more readily than that of an ethyl group.

Malonic and acetoacetic esters are alkylated by the oxonium salts. The reactions between the sodium derivatives of malonic ester and of acetoacetic ester and triethyloxonium borofluoride in alcoholic solution produced the corresponding *C*-ethyl derivatives in yields of 35.8 and 46.7%, respectively.

The polymerization of epichlorohydrin has been effected by tertiary oxonium salts.[150] In benzene solution up to 64 moles of epichlorohydrin were polymerized by 1 mole of triethyloxonium borofluoride. The molecular weight of the product indicated that each polymer molecule contained 5 to 6 epichlorohydrin units.

IX. FACTORS LIMITING INDUSTRIAL USE OF BORON FLUORIDE

The use of boron fluoride catalysis for chemical reactions which have been described has been valuable in many cases for obtaining results impossible to reach by employing as catalysts similar metal or non-metal halides. There must be many interesting reactions with boron fluoride and its complexes undiscovered and unreported as yet; so that the field of boron fluoride catalysis is far from being closed.

Up to the present time limited use for boron fluoride has been found in industrial processes. On account of its relatively high price it has been employed economically only in strictly catalytic processes, in which any quantity of the product can be obtained theoretically with a small amount of the catalyst. Some technical application for carrying out reactions in which boron fluoride is removed from the reaction by complex formation with a product has been made, but it must be possible to regenerate the boron fluoride satisfactorily from the complex. Such processes for the regeneration of the catalyst have been disclosed by du Pont[151] and Standard Oil Development Co.[152] According to the du Pont patent boron fluoride dihydrate is treated with calcium fluoride at temperatures up to 150°C. with the production of calcium borofluoride, $Ca(BF_4)_2$, from which the boron fluoride can be distilled at 300° to 500°C. The Standard Oil Development Co. process involves the combination of the boron fluoride with gaseous ammonia, filtration of the precipitated boron fluoride-ammonia, $NH_3 \cdot BF_3$, and decomposition of the complex by sulfuric acid and expulsion of the boron fluoride at 190° to 200°C. The recovery of the catalyst is effected in a yield of 75%. These methods, however, are not always entirely satisfactory when they are applied technically, so that there are still many problems awaiting solution in this field.

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[150] Kroning, Thesis, Marburg, 1936, p. 16.

[151] E. I. du Pont de Nemours and Co., French Patent 814,839; U. S. Patents 2,135,460 and 2,160,575; Dutch Patent 46,391; British Patent 502,680.

[152] Standard Oil Development Co., U. S. Patent 2,167,358. See also reference cited in foot-note 23.

Use of Hydrogen Fluoride in Organic Reactions

By KURT WIECHERT

Translated and revised by J. Elmore Jones

I. INTRODUCTION

Since anhydrous hydrogen fluoride was made available commercially a little over a decade ago, it has been employed to an ever increasing extent in reactions involving organic compounds. It adds to olefins in the same way as do the other hydrogen halides with the formation of fluorides; however, by far the most important use of hydrogen fluoride is due to its powerful dehydrating action which has led to its replacement of sulfuric acid in many condensation reactions. Sulfuric acid has the disadvantage of causing sulfonation and oxidation reactions to proceed simultaneously with the condensation reactions, particularly in reactions involving aromatic compounds, while hydrogen fluoride rarely causes the fluorination of aromatic nuclei and tarry residues are almost never formed. The replacement of other catalysts such as boron fluoride, aluminum chloride, and other metal halides by hydrogen fluoride has been most successful; hydrogen fluoride has the advantage of rarely causing the coupling of aromatic nuclei, and it does not catalyze the migration of alkyl groups. Liquid hydrogen fluoride has proved to be an excellent solvent for a large number of organic compounds; it permits such reactions as nitration, sulfonation, fluorination, and diazotization to be carried out in homogeneous media.

Hydrogen fluoride has a number of other advantages which make its use highly desirable both in laboratory and industrial processes. By the proper control, side reactions can be kept to a minimum, so that better yields of purer compounds may be obtained. The use of hydrogen fluoride often leads to the preparation of substances by reactions which either are not catalyzed by the usual reagents or are uneconomical. The gas is easily liquefied, and it boils at a temperature (19.5°C.) high enough that reactions can be carried out in the liquid at atmospheric pressure. Yet the boiling point is low enough so that hydrogen fluoride can be removed from the reaction mixture by a simple distillation, thus facilitating not only the isolation of the products of the reaction (or of unchanged starting material) but also the recovery of the catalyst. The stability of hydrogen fluoride makes possible its use over a wide range of temperatures and pressures. This, coupled with the fact that the anhydrous acid is practically non-corrosive to the steels commonly used in industrial equipment, makes it most suitable for commercial processes.[1,2]

Following a short discussion of the preparation and properties of hydrogen fluoride, its use in fluorination reactions, in the degradation and synthesis of organic compounds, and as a solvent will be considered. Since the value of a presentation of this type depends on its completeness, the inclusion of the patent literature has been considered advisable.

II. PREPARATION, PURIFICATION, AND METHOD OF HANDLING HYDROGEN FLUORIDE

The method used in the laboratory for the preparation of small amounts of hydrogen fluoride is the pyrolysis of potassium bifluoride. According to Fredenhagen and Cadenbach,[3] evolution of the gas begins at 400°C. About 30% of the hydrogen fluoride is given off as the temperature is increased to 504°, at which point the temperature and the composition of the melt remain constant and a precipitate of solid potassium fluoride begins to form. After this point has been reached, the heating of the retort must be moderated somewhat or the reaction is likely to become too vigorous. In order to obtain very dry hydrogen fluoride it is essential that the potassium bifluoride be dried carefully before being pyrolyzed. This is done by heating the salt to 150°C. in a current of dry air. Even after this treatment some traces of water are left, and the first fraction of hydrogen fluoride, with which it distils, must be discarded. Simons dried the potassium bifluoride by electrolysis of the molten salt until the evolution of fluorine gas indicated that all the water had been decomposed.[4]

The industrial method for the preparation of hydrogen fluoride consists of allowing a high grade fluorspar (calcium fluoride) to react with concentrated sulfuric acid under carefully controlled conditions at an elevated temperature (300° to 800°C.). The sulfuric acid can be replaced by fluorosulfonic acid, phosphoric acid, or by acid sulfates.[5] Another method, which has not been particularly valuable, involves the decomposition of fluorides with steam at high temperatures and pressures, as illustrated in the following equation:

$$CaF_2 + 2H_2O \longrightarrow 2HF + Ca(OH)_2$$

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[1] Simons, *Ind. Eng. Chem.*, **32**, 178 (1940).

[2] Linn and Grosse, *Ind. Eng. Chem.*, **37**, 924 (1945).

[3] K. Fredenhagen and Cadenbach, *Z. anorg. allgem. Chem.*, **178**, 289 (1929); K. Fredenhagen, German Patent, 490,103.

[4] Simons, *J. Am. Chem. Soc.*, **46**, 2179 (1924); *Inorganic Syntheses*, McGraw-Hill, New York, 1939, Vol. I, p. 134.

[5] E. I. du Pont de Nemours and Co., U. S. Patent, 2,047,210.

Other salts which have been used are ferrous fluoride[6] and silicon tetrafluoride.[7]

The crude hydrogen fluoride obtained by the fluorspar process may contain as high as 10% of impurities, of which water and silicon tetrafluoride are the chief ones. The others present in smaller quantities are sulfuric acid, fluorosulfonic acid, sulfur dioxide, and sulfur trioxide. One of the most common methods for the purification of the product consists of passing the gas into fuming sulfuric acid maintained at a low temperature by external cooling. Hydrogen fluoride, water, sulfur trioxide, and fluorosulfonic acid are dissolved easily, but silicon tetrafluoride and sulfur dioxide are not. By heating the sulfuric acid solution to 60° to 100°C., the hydrogen fluoride is expelled; it contains at most only traces of sulfur dioxide.[8] Methods involving fractional condensation or distillation are particularly valuable for the removal of water and silicon tetrafluoride[9]; the temperature is adjusted so that the greatest possible difference in the partial pressures of hydrogen fluoride and water vapor over the liquid is obtained.[10] The commercial method, in which fractionation is used for the purification of gaseous products of the calcium fluoride reaction, affords hydrogen fluoride which contains 0.1 to 0.2% of water, less than 0.1% of silicon tetrafluoride, and slight traces of sulfur dioxide.

Small quantities of hydrogen fluoride may be purified in the laboratory by condensing the crude gas over a solid alkali fluoride at 15°C. The liquid polyfluoride ($NaF \cdot 4.5HF$) which is obtained is removed and subjected to thermal decomposition.[11] In a similar process, which is more troublesome, however, the alkaline earth silicofluorides[12] are used.

None of the usual drying agents, such as sulfuric acid, calcium chloride, and phosphorus pentoxide, can be used for the dehydration of hydrogen fluoride, since they react with it. One drying method consists of mixing the gas with fluorine, which reacts with any water vapor present and produces hydrogen fluoride.[13] A much simpler method is that of dropping thionyl chloride into liquid hydrogen fluoride. The hydrogen chloride

$$SOCl_2 + 2HF \longrightarrow SOF_2 + 2HCl$$

$$SOF_2 + H_2O \longrightarrow 2HF + SO_2$$

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[6] Sherwin-Williams Corporation, U. S. Patent, 2,167,784.

[7] Societá Anonima Processi Privative Industriali, Italian Patent, 355,502; *Chem. Zentr.*, 1941, II, 2982.

[8] I. G. Farbenindustrie A.-G., British Patent, 387,614; French Patent, 741,966.

[9] E. I. du Pont de Nemours and Co., U. S. Patents, 2,018,397, 2,047,210; I. G. Farbenindustrie A.-G., British Patent, 357,438; U. S. Patent, 1,851,652; Verein für Chemische und Metallurgische Produktion, British Patent, 289,383.

[10] Bishop, U. S. Patent, 2,088,048.

[11] I. G. Farbenindustrie A.-G., German Patent, 558,465.

[12] Meyrhofer, U. S. Patent, 1,701,225; Buchner, British Patent, 234,852.

[13] I. G. Farbenindustrie A.-G., British Patent, 363,424.

formed is very insoluble in hydrogen fluoride and escapes from the liquid, but traces of sulfur dioxide remain which can be eliminated if necessary only by fractionation. These traces of sulfur dioxide do not necessarily have to be removed, since most reactions are not affected adversely by it. An excess of thionyl chloride, however, must be avoided.[14]

Pure hydrogen fluoride is a clear, water-white liquid which boils at 19.5°C. and solidifies at −83°. The smallest conductivity[15] which has been determined for it is 1×10^{-5}. Liquid hydrogen fluoride fumes strongly in air, is very hygroscopic, and reacts violently with water or ice. A number of hydrates are known. This extreme tendency to absorb water makes it advisable to distil the gas (instead of pouring the liquid) into a reaction vessel when perfectly dry hydrogen fluoride is needed for a reaction.

Only platinum and platinum-gold alloys are suitable materials for containers for use in exact work. When hydrogen fluoride has stood for several days in a silver flask, the presence of silver fluoride can be detected in it. Copper vessels can be used, but it must be kept in mind that when a copper flask is heated (to remove adsorbed moisture) it acquires a layer of oxide with which hydrogen fluoride will react with the formation of water and copper fluoride. Other materials which are suitable for use in the reactions to be described later are certain types of steel, sintered corundum, paraffin (with which the removal of the moisture film is impossible), and bubble-free quartz. Quartz dissolves in liquid hydrogen fluoride to the extent of only 1% in 4 hours, and containers made from it can be used for processes in which the reaction time is short. Materials recommended for the construction of industrial equipment in which anhydrous or nearly anhydrous hydrogen fluoride is employed are nickel,[16] aluminum,[17] Monel metal,[18] cupronickel,[19] wrought iron,[20] and chrome, molybdenum, and nickel steels.[18,21,22]

The corrosion of metals by hydrogen fluoride increases with increasing temperature. The rapid corrosion of stainless steel and copper makes them unsatisfactory materials for the construction of equipment for processes in which the temperatures involved are greater than 200°C. Metals used successfully for tubing are tin and silicon bronzes, red brass, and a brass consisting of 70% copper, 29% zinc, and 1% tin.[19] All-metal apparatus equipped with tightly fitting ground plugs has been used industrially for batch processes. The metal plugs were lubricated with pure graphite before use. Plugs of sulfur or sintered corundum have also been used; they were coated with a mixture of wax and rubber.

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[14] Wiechert, unpublished observations.

[15] K. Fredenhagen and Cadenbach, *Z. physik. Chem.*, Abt. A, **146**, 245 (1930).

[16] E. I. du Pont de Nemours and Co., U. S. Patent, 2,174,118.

[17] Grosse and Linn, *J. Org. Chem.*, **3**, 26 (1938).

[18] Kinetic Chemicals, Inc., U. S. Patent, 2,005,710; *Hydrofluoric Acid Alkylation*, Phillips Petroleum Co., Bartlesville, Oklahoma, 1946, pp. 267 *et seq.*

[19] Holmberg and Prange, *Ind. Eng. Chem.*, **37**, 1030 (1945).

[20] Calcott, Tinker, and Weinmayr, *J. Am. Chem. Soc.*, **61**, 949 (1939).

[21] E. I. du Pont de Nemours and Co., British Patent, 406,284.

[22] Fehr *Chem. & Met. Eng.* **50**, No. 11, 129 (1943).

A generalized procedure for carrying out organic reactions is as follows: Hydrogen fluoride is distilled from a generator or passed from a steel cylinder into a flask immersed in a cooling bath. Moisture from the air is carefully excluded during this process. If for some reactions it is necessary to equalize the pressure with that of the atmosphere, an equalizer is constructed from a long copper tube filled with granulated anhydrous potassium fluoride. The residue from the generation of hydrogen fluoride from potassium bifluoride is quite suitable for this purpose. Solid substances are added most conveniently as pellets, since in that form they can be added quickly and less moisture can enter the system. Liquids are introduced by dropping funnels.[23] At the end of the reaction the hydrogen fluoride can be recovered for further use by distillation or by being evaporated in a current of dry air. The residue is dissolved in a suitable solvent and the last traces of hydrogen fluoride are removed by the addition of alkali or a carbonate (calcium carbonate). The reaction mixture can also be worked up by pouring the solution carefully on ice, but in that case the recovery of the hydrogen fluoride is not practical.

The metal apparatus is dried before use by heating it above 100°C. and cooling in a desiccator over sulfuric acid. All reagents must also be dried carefully. Since some reactions give entirely different products when 96% hydrogen fluoride is used in place of the anhydrous acid, the exclusion of moisture is essential. Usually in such cases the yields drop with increasing water content. Fortunately, however, a very large number of reactions, and especially those carried out on an industrial scale, are relatively unaffected by small quantities of water, and these elaborate precautions for the exclusion of moisture are unnecessary. In some cases water has been shown to have a catalytic effect.

Rubber gloves must always be worn when hydrogen fluoride is being handled, and care must be taken that no acid comes in contact with the skin. Highly concentrated solutions of hydrogen fluoride cause painful and very slow-healing burns. If some is spilled on the skin, it is not sufficient merely to wash the parts with water or alkali. A salve containing magnesium oxide and glycerol (or better, calcium gluconate) must be rubbed into the skin immediately. In cases of severe burns a subcutaneous injection of calcium gluconate-lactobionate (Calcium-Sandoz) should be made as soon as possible. This treatment is necessary to neutralize the acid and to precipitate the fluoride ion as quickly as possible in order to minimize the extent and painfulness of the burns. If adequate precautions are taken, no serious accidents should occur; some industrial plants using liquid hydrogen fluoride have had excellent safety records.[24]

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[23] K. Fredenhagen and H. Fredenhagen, *Z. anorg. allgem. Chem.*, **243**, 39 (1940).

Gaseous hydrogen fluoride is somewhat dangerous also, since in high concentrations it irritates the mucous membranes and prolonged exposure causes mild burns on sensitive areas of the skin.

III. PREPARATION OF FLUORINE COMPOUNDS BY USE OF HYDROGEN FLUORIDE

1. Addition of Hydrogen Fluoride to Unsaturated Compounds

A. Addition to Olefins

The tendency for a hydrogen halide to add to an olefin decreases from hydrogen iodide to hydrogen chloride, and early reports indicated that hydrogen fluoride was incapable of adding to a carbon-carbon double bond.[25] Sun and Sze claimed that quantum mechanical considerations showed the reaction to be impossible,[26] but in spite of this a method has been developed for the preparation of alkyl fluorides by the addition of hydrogen fluoride to alkenes.[17,27]

In connection with some work on the direct addition of an olefin to a paraffin hydrocarbon under the influence of boron fluoride and hydrogen fluoride, Grosse and Linn discovered that hydrogen fluoride added to ethylenic double bonds. They investigated its reactions with ethylene, propylene, and cyclohexene at temperatures ranging from −60° to 90°C. and at pressures from 3 to 10 atmospheres.[17] The reactions were carried out by introducing a predetermined quantity of anhydrous hydrogen fluoride into a bomb constructed of allegheny metal and then forcing the olefin in under pressure. The best yields of alkyl fluorides obtained from these olefins were as follows: ethyl fluoride 81%, isopropyl fluoride 62%, and cyclohexyl fluoride 80%. The addition followed Markovnikov's rule. The presence of nickel, copper, aluminum, boron fluoride, and steel had no effect on the reactions, but fluorides of zinc, aluminum, manganese, copper, and iron have been recommended as catalysts in a patent specification.[21]

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[24] K. Fredenhagen and H. Fredenhagen, *Angew. Chem.*, 52, 189 (1939). Safety precautions to be observed when handling hydrogen fluoride and directions for first aid in case of accident are described more fully in *Hydrofluoric Acid Alkylation*, Phillips Petroleum Co., Bartlesville, Oklahoma, 1946, pp. 234 *et seq.*

[25] Bockemüller, *Organische Fluorverbindungen*, Enke, Stuttgart, 1936, pp. 34, 35; Edwards, Ann Arbor, 1945.

[26] C. E. Sun and C.-H. Sze, *J. Chinese Chem Soc* . 5, 1 (1937); *Chem. Zentr.*, 1937, I, 4217; *Chem. Abstracts*, 31, 4192 (1937).

[27] See the chapter by Bockemüller on fluorine compounds (page 229).

The formation of polymers and hydrofluorinated polymers by a competing reaction was increased as higher temperatures were used for the addition, and in some cases the polymer was the main product. Thus, it is preferable to carry out the reactions at temperatures of −25° to −60°C.[28] The use of catalysts, however, allows the addition to proceed satisfactorily at elevated temperatures (ethylene 100°, butylene 100° to 200°, propylene 250°).[21] Grosse and Linn found that these polymeric products were the result of a reaction between the alkyl fluorides and excess hydrogen fluoride, a reaction which takes place with all the alkyl fluorides except ethyl fluoride. The yields in the case of ethylene increased with increasing temperature, but those of the other two olefins decreased, perhaps because of polymer formation.

The reaction was also applied to cyclopropane[17] by adding the hydrocarbon successively to a system containing an excess of hydrogen fluoride. Since much heat was evolved after each addition, adequate temperature control to 25°C. was difficult. Under the best conditions the product consisted of 80% of *n*-propyl fluoride and 8% of isopropyl fluoride. The isomerization into the iso compound was due at least partly to the lack of proper control of the reaction. The best yields were obtained in reactions in which the period of contact with hydrogen fluoride was not longer than 15 minutes.

The same general method was used for the preparation of *sec*-butyl, *tert*-butyl, and *tert*-amyl fluorides from 1-butene, isobutylene, and trimethylethylene.[29,30] Reactions between cyclohexene and cyclohexanol in hydrogen fluoride gave yields of cyclohexyl fluoride as high as 61.5% along with small quantities of dicyclohexyl ether.[31]

The use of high pressures and temperatures for these reactions has been disclosed in the patent literature.[21,32] The higher members of a series of alkenes seem to react more easily than the lower ones,[21,28] and solvents such as hexane,[21] carbon tetrachloride, and methylene chloride[33] appear to favor the reaction. According to a patent of Kinetic Chemicals, Inc., chlorine catalyzes the addition reaction and produces mixed halogenated products.[34] It may be that in this case chlorine adds to the double bond first and that the chlorohydrocarbon is converted to the fluoride by hydrogen fluoride.

Little is known about the limits of this reaction for obtaining alkyl fluorides. The addition of hydrogen fluoride to butadiene and decylene and to oxygen-containing compounds such as ricinoleic, undecylenic, and oleic acids as well as oleyl alcohol has been accomplished.[33] According to Klatt, however, olefins which have an oxygen atom attached to a carbon atom in the immediate vicinity of the double bond neither add hydrogen fluoride nor polymerize in its presence.[35] Allyl alcohol and cinnamic acid are examples of such compounds.

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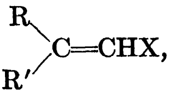
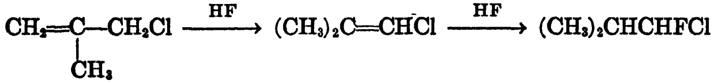
[28] Universal Oil Products Co., U. S. Patent, 2,220,713.
[29] Grosse, Wackher, and Linn, *J. Phys. Chem.*, **44**, 275 (1940).
[30] Simons and Bassler, *J. Am. Chem. Soc.*, **63**, 880 (1941).
[31] Simons and Meunier, *J. Am. Chem. Soc.*, **63**, 1921 (1941).
[32] Standard Oil Development Co., U. S. Patent, 2,090,772.
[33] I. G. Farbenindustrie A.-G., French Patent, 799,432.
[34] Kinetic Chemicals, Inc., U. S. Patent, 2,005,707.

Recently the addition of hydrogen fluoride to olefins already containing halogen atoms has been studied somewhat extensively. It was found that the reactions with only certain types of monohaloolefins gave good yields of clean products. Simons and Plueddeman found that the monohaloolefins could be divided conveniently into three types, depending on the way in which they reacted with hydrogen fluoride.[36,37]

Those of Type I, RCH═CHX, did not react well and did not give clean products. At room temperature no apparent combination with hydrogen fluoride took place, and the mixtures of products obtained at higher temperatures were contaminated with tars, the amount of which increased with the temperature of the reaction. 1-Chloro-1-propene reacted with hydrogen fluoride at 100°C. in 4 hours with the formation of 1-chloro-2-fluoropropane (20%), 1-chloro-1-fluoropropane (10%), 1,1-difluoropropane (traces), 1,2-dichloropropane (20%), and considerable amounts of tar. A small amount (5%) of unchanged olefin was recovered. The reaction with 1-chloro-1-butene at 65° was poorer than that with the lower homologue. More tar was formed and 25% of the starting material was recovered.

Monohaloolefins of type II,  $\overset{R}{\underset{R'}{>}}C{=}CHX$, added hydrogen fluoride readily at low temperatures (−23° to 0°C.) in accordance with Markovnikov's rule, and negligible amounts of tar were formed. Both isocrotyl chloride (II) and methallyl chloride (I) gave good yields of 1-chloro-1-fluoro-2-methylpropane (III). In the latter case the methallyl chloride



$$\underset{\text{(I)}}{CH_2{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}CH_2Cl} \xrightarrow{HF} \underset{\text{(II)}}{(CH_3)_2C{=}CHCl} \xrightarrow{HF} \underset{\text{(III)}}{(CH_3)_2CHCHFCl}$$

undoubtedly was isomerized rapidly to isocrotyl chloride before the addition of the hydrogen fluoride took place.[36]

The addition of hydrogen fluoride to monohaloolefins of type III,

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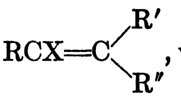
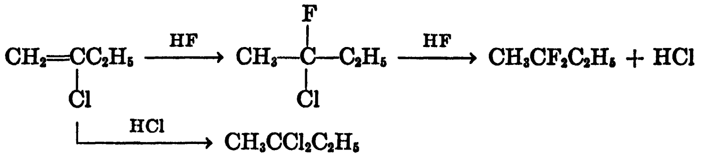
[35] Klatt, *Z. anorg. allgem. Chem.*, 222, 225 (1935).
[36] Simons and Plueddeman, *J. Am. Chem. Soc.*, 65, 1271 (1943).

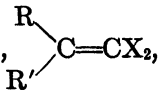
 $RCX{=}C(R')(R'')$, was found to proceed with extreme rapidity at low temperatures.[36–38] The reaction did not stop with simple addition of the acid, but the halogen atom was replaced also by hydrogen fluoride with the production of the difluoro compounds in yields of 59 to 70%. The hydrogen chloride liberated in the halogen exchange reaction was added to some of the unchanged starting material with the production of the corresponding dichloro compounds in yields as high as 25%. The reaction, which proceeded quite smoothly and gave practically no tarry by-products, has been applied to a series of monochloroolefins from 2-chloro-1-propene to 2-chloro-2-octene. Extreme care had to be observed to prevent the reaction from becoming too vigorous. The olefin and anhydrous hydrogen fluoride precooled to −78°C. were mixed in an autoclave and allowed to warm up slowly to a final temperature of 35° to 46°. The pressure of the system was maintained at 4 to 11 atmospheres by letting the hydrogen chloride escape through a condenser cooled by dry ice. The increase in pressure was used as an indication of the rate of the reaction and the rate of heating was adjusted accordingly. If the hydrogen chloride was not removed gradually, the amount of dichloro compound was increased.[38]



$$CH_2{=}CClC_2H_5 \xrightarrow{HF} CH_3CFClC_2H_5 \xrightarrow{HF} CH_3CF_2C_2H_5 + HCl$$

$$CH_2{=}CClC_2H_5 \xrightarrow{HCl} CH_3CCl_2C_2H_5$$

In contrast to the results obtained with simple monohaloolefins of type III, 1,2-dichloro-2-propene added hydrogen fluoride and gave 1,2-dichloro-2-fluoropropane, $CH_3CClFCH_2Cl$. Very little subsequent substitution took place. From 1 mole of the olefin were obtained 0.74 mole of the monofluoride and 0.04 mole of the difluoride, and 0.10 mole of unchanged olefin was recovered. In this case the adjacent chlorine atom so stabilizes the chlorine atom on the carbon atom to which the fluorine atom is added that its exchange with hydrogen fluoride is minimized.[39]

Asymmetric dihaloolefins,  $(R)(R')C{=}CX_2$, combined with hydrogen fluoride smoothly at 65°C. with little substitution. 1,1-Dichloroethylene reacted with 4 moles of hydrogen fluoride in 3 hours at 65° with the formation

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[37] Henne and Hinkamp, *J. Am. Chem. Soc.*, **67**, 1194, 1198 (1945).
[38] Renoll, *J. Am. Chem. Soc.*, **64**, 1115 (1942).
[39] Henne and Haeckl, *J. Am. Chem. Soc.*, **63**, 2692 (1941).

of 1,1-dichloro-1-fluoroethane (50%), 1,1,1-trichloroethane (5%), traces of 1-chloro-1,1-difluoroethane, and 15% of tar. Only 10% of unchanged olefin was recovered. Reactions with 1,1-dichloro-1-propene,[40] 1-chloro-1-fluoro-1-propene,[40] 1,1-dichloro-1-butene, and 1,1-dichloro-2-methyl-1-propene have also been studied. At elevated temperatures tar formation becomes the dominating reaction.[36]

Symmetrical dihaloolefins, RCX═CXR′, gave contradictory results. Hydrogen fluoride could not be made to react with 1,2-dichloroethylene under any conditions, while *cis*- and *trans*-1,2-dichloro-1-propene added the gas smoothly at 120°C. to produce the same addition product, CH_3-$CFClCH_2Cl$, and some of the substitution product, $CH_3CF_2CH_2Cl$. The *trans*-olefin consistently gave higher yields of the substitution product. Hydrogen fluoride added more readily to *trans*-1-chloro-2-fluoro-1-propene than to the *cis* form; the product in both cases was 1-chloro-2,2-difluoropropane.[36]

Trichloroethylene and its next higher homologue were recovered unchanged from reaction mixtures heated to temperatures as high as 160°C. At low temperatures perchloroethylene and hexachloropropylene did not add hydrogen fluoride and could be recovered unchanged, but at higher temperatures substitution of the —CCl_3 group in the hexachloropropylene began to take place.[36]

Recently the use of hydrogen fluoride for replacing the halogen atoms in organo-silicon chlorides by fluorine atoms has been reported. Various alkylfluorosilanes which were prepared and the yields obtained are as follows: di-*n*-butyldifluorosilane (70%), tri-*n*-butylfluorosilane (50%), *n*-butyltrifluorosilane (40%), tri-*n*-amylfluorosilane (70%), di-*n*-amyldifluorosilane (80%), *n*-amyltrifluorosilane (40%). The yields of the methyl- and phenylfluorosilanes were not determined but appeared to be of the same general magnitude.[41]

B. Addition to Acetylenes

Only a small amount of work on the addition of hydrogen fluoride to acetylenic compounds has been published. Grosse and Linn[42] succeeded in preparing 1,1-difluoroethane, 2,2-difluoropropane, 2,2-difluorobutane, 2,2-difluoropentane, 2,2-difluorohexane, 3,3-difluorohexane, and 2,2-difluoroheptane from the corresponding alkynes in yields averaging 65%.

$$RC\equiv CH \xrightarrow{HF} RCH{=}CHF \xrightarrow{HF} RCH_2CHF_2$$

The products were always those expected from Markovnikov's rule. Only in the case of acetylene, with which the reaction required high pressures and a long period of contact with hydrogen fluoride at room temperature, was an unsaturated monofluoride (vinyl fluoride) obtained. The other acetylenes reacted instantly and completely at low temperatures (−70°C.), and only the saturated difluorides were formed. Some alkyne polymers appeared as by-products. Vinylacetylene gave no monomeric addition product.

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[40] Henne and Whaley, *J. Am. Chem. Soc.*, **64**, 1157 (1942).
[41] Pearlson, Brice, and Simons, *J. Am. Chem. Soc.*, **67**, 1769 (1945).
[42] Grosse and Linn, *J. Am. Chem. Soc.*, **64**, 2289 (1942); Universal Oil Products Co., U. S. Patent, 2,287,934.

The method used by Grosse and Linn for the addition of hydrogen fluoride to alkylacetylenes has been modified by Henne and Plueddeman,[43] who found that changes in the procedure were necessary for large scale preparations. The purpose of the changes was to prevent the formation of localized hot spots which caused resinification and of cold spots where the reagents tended to accumulate without reacting. Low boiling alkynes such as 1-butyne were allowed to boil slowly and the gas was passed into a 25% excess of liquid hydrogen fluoride in a copper flask cooled in ice. After 1 hour the volatile contents of the flask were allowed to evaporate, and the residue was poured on ice, worked up, and distilled. Yields of difluoride averaging 75% were obtained, along with about 18% of oily residues. Pentyne and hexyne were added to the hydrogen fluoride dropwise at −50°C., and the reaction mixture was allowed to warm to room temperature before being worked up.

A solution of hydrogen fluoride in an ether or a ketone was used as the hydrofluorination agent with higher boiling alkynes. The oxonium salts formed by hydrogen fluoride are good solvents both for the reagents and the products. Since the 2 moles of acid attached to the oxygen atom are unavailable for addition, an excess must be used. The yields obtained approached 90% as the reaction time was increased. No resinous or tarry materials resulted from these procedures.

When a second chemical function was present in the molecule, difficulties developed. 1,8-Nonadiyne in an oxygenated solvent gave a mixture of 2,2,8,8-tetrafluorononane and 2,8-difluoronona-1,8-diene but 1,6-heptadiyne was resinified completely.

Reactions with other substituted acetylenes have been reported in the patent literature (acetylenedicarboxylic acid, phenylpropiolic acid, and stearolic acid from which 9,10-difluorostearic acid has been made).[44] When the reaction is carried out in the gas phase, a catalyst consisting of a halide or oxide of mercury precipitated on charcoal is used.[45] The reaction is exothermic and in certain cases the dilution of the reactants with an inert gas or the addition of a solvent such as methylene chloride or carbon tetrachloride is necessary in order to keep it under control.

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[43] Henne and Plueddeman, *J. Am. Chem. Soc.*, **65**, 587 (1943).
[44] I. G. Farbenindustrie A.-G., German Patent, 621,977.
[45] I. G. Farbenindustrie A.-G., German Patent, 641,878.

C. Addition to Other Unsaturated Systems

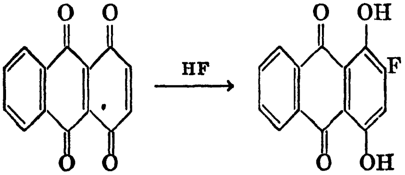
A few instances of the reaction of hydrogen fluoride with other unsaturated compounds are known. The reaction of ketene with hydrogen fluoride is strongly exothermic and takes place either in the gas phase or in an indifferent solvent.[46] The product is acetyl fluoride, a surface-active substance. If the temperature of the reaction mixture becomes too high, only polymeric products can be isolated.

$$CH_2{=}C{=}O + HF \longrightarrow CH_3COF$$

E. I. du Pont de Nemours & Company has worked out an entirely new method for the production of fluoroacetic acid from carbon monoxide, hydrogen fluoride, and formaldehyde. Excess carbon monoxide is introduced into molar quantities of the other two reagents at 160°C. and under 750 atmospheres pressure. It is important that no water be present, since it would cause the formation of the hydroxy acid.[47] A reaction which appears to be somewhat similar to this is the production of organic acids from carbon monoxide, hydrogen fluoride, and alcohols or alkyl halides.[48] The presence of methanol or water in the reaction mixtures was necessary for the production of the acids from alkyl halides. Although acid fluorides were thought to be the intermediates in the reaction, experiments carried out in an attempt to establish a mechanism were inconclusive.

$$CO + HCHO + HF \longrightarrow CH_2FCOOH$$

The addition of hydrogen fluoride to quinones with the production of hydroxyaryl fluorides has been successful in only one case. Dimroth and Hilcken obtained a 75% yield of 2-fluoroquinizarin from anthradiquinone,[49] but benzoquinone afforded only black tars.[50]



The carbon-nitrogen double bond will also add hydrogen fluoride.

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[46] Eschenbach, German Patent, 638,441.
[47] E. I. du Pont de Nemours and Co., British Patent, 527,644.
[48] Simons and Werner, *J. Am. Chem. Soc.*, **64**, 1356 (1942).
[49] Dimroth and Hilcken, *Ber.*, **54**, 3056 (1921).
[50] Levy and Schultz, *Ann.*, **210**, 144 (1881).

Linhard and Betz passed cyanic acid into a solution of hydrogen fluoride in ether at −80°C. and obtained carbamic acid fluoride.[51]

$$HNCO + HF \longrightarrow H_2NCOF$$

2. Preparation of Fluorides from Halides

A. In Presence of Catalysts

The simplest method of preparing organic fluorine compounds, the direct replacement of another halogen atom by fluorine by means of the action of hydrogen fluoride alone, is effective only in a few cases. Generally a catalyst such as a heavy metal halide is necessary, and in those cases it is questionable whether the process is a true catalytic one (Eq. 1) or whether

$$RCl + HF \xrightarrow{MCl} RF + HCl \qquad (1)$$

the fluorination is effected by the heavy metal fluoride formed by the reaction between the metal halide and hydrogen fluoride. In the latter case the hydrogen fluoride does not cause the fluorination by a direct interchange of halogen with the organic halide, but it merely serves the purpose of forming and regenerating the active agent (Eqs. 2 and 3).

$$MCl + HF \longrightarrow MF + HCl \qquad (2)$$

$$RCl + MF \longrightarrow RF + MCl \qquad (3)$$

The preparation of alkyl fluorides can be carried out by a simple method devised by Fredenhagen, who dissolved silver carbonate in hydrogen fluoride and then added the alkyl chloride; a double displacement type of reaction occurs and the alkyl fluoride and silver chloride are formed.[52] The limits of this reaction are not known. Simons and Herman[53] used anhydrous silver fluoride in liquid hydrogen fluoride for the fluorination of ω-dibromoacetophenone and obtained the corresponding difluoro compound in a yield of 40%; there was no indication that any of the mixed fluorobromo compound had been formed. When this reaction was extended to trichloroacetophenone, however, no trifluoroacetophenone could be isolated, but the reaction mixture gave ω-dichlorofluoroacetophenone (48.7%) and ω-chlorodifluoroacetophenone (8.5%).

$$RCl + AgF \longrightarrow RF + AgCl$$

$$C_6H_5COCHBr_2 + 2HF \longrightarrow C_6H_5COCHF_2 + 2HBr$$

$$C_6H_5COCCl_3 \xrightarrow{HF} C_6H_5COCl_2F + C_6H_5COClF_2$$

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[51] Linhard and Betz, *Ber.*, 73, 181 (1940).

[52] K. Fredenhagen, *Z. Elektrochem.*, 37, 684 (1931). See the chapter by W. Bockemüller on organic fluorine compounds (page 229).

[53] Simons and Herman, *J. Am. Chem. Soc.*, 65, 2064 (1943).

A method of fluorination developed by Henne involves the introduction of hydrogen fluoride into a suspension of mercuric oxide in the alkyl halide with the formation of nascent mercuric fluoride, which effects the reaction.[54] The reaction takes place instantaneously at room temperature and is so strongly exothermic that adequate means of cooling the mixture have to be provided to keep the reaction under control. The yields of the fluoro compounds are generally from 70 to 80%. The removal of hydrogen halide does not take place.

Hydrogen fluoride appears to be unable to replace 3 chlorine atoms on one carbon atom except for the aryl trichloromethyl compounds, the halogen atoms of which are usually replaceable even in the absence of catalysts. The production of diphenyldifluorodichloroethane from diphenyltetrachloroethane by this method takes place at 50° to 60°C., but other compounds of the same type require the use of antimony fluorides to catalyze the reaction with hydrogen fluoride.[55]

The catalysts used industrially for the reaction between alkyl halides and hydrogen fluoride are the fluorides of the heavy metals and particularly those of antimony. Chromic fluoride is a true catalyst, since it does not cause fluorination by itself but promotes the replacement of halogen atoms by hydrogen fluoride.[56] The reaction is carried out by passing a mixture of the alkyl chloride and hydrogen fluoride over a catalyst consisting of a mixture of carbon, 5 to 15% of chromium fluoride, and a little chromic oxide. The degree of fluorination increases with the quantity of hydrogen fluoride mixed with the organic halide and with the temperature (350° to 550°C.).

This type of reaction has been the subject of numerous patents assigned to Kinetic Chemicals, Inc. Two different methods have been worked out for effecting the replacement, involving fluorination in gaseous and in liquid phases. Solid catalysts supported by a grating in an electrically heated tube are used in the first process,[18,34,57] and over them are passed the gaseous starting materials, which in certain cases are mixed previously. The fluorides and chlorides of the following metals are in demand for catalysts (the iodides and bromides are less suitable for this purpose): Na, Cu, Ag, Ca, Cd, Zn, Hg, Pb, V, Sb, U, Mn, Fe, Ni, Co, and Pt.[58] The chlorides are partly converted to the fluorides during the course of the reaction. The replacement requires lower temperatures and the yields are better when the metal halide is mixed in a ratio of 1:10 with a non-specific surface active substance. Carbon tetrachloride does not react with hydrogen fluoride over either copper chloride or porous sintered corundum even at 400°C., but, when the salt and the corundum are mixed, the fluorination proceeds readily at 250°. Over either ferric chloride or charcoal only a slight reaction takes place at 100°, but a 70 to 90% yield of the fluorination product is obtained with a mixture of the two substances.[59] The most favorable temperatures for effecting these reactions are usually between 250° and 450°.[57] The presence of small quantities of water has no effect on the fluorination.

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[54] Henne, *J. Am. Chem. Soc.*, 60, 1569 (1938); Henne, Renoll, and Leicester, *ibid.*, 61, 938 (1939); Henne, in *Organic Reactions*, Wiley, New York, 1944, Vol. II, p. 56.

[55] E. I. du Pont de Nemours and Co., U. S. Patent, 2,238,242.

[56] Imperial Chemical Industries, Ltd., British Patent, 468,447; U. S. Patent, 2,110,369.

[57] Kinetic Chemicals, Inc., U. S. Patents, 2,062,743, 2,058,453.

[58] Kinetic Chemicals, Inc., U. S. Patents, 2,005,709, 2,005,711.

In the second method, the reaction of alkyl halides in the liquid phase with hydrogen fluoride is catalyzed by a mixture of antimony chlorofluorides.[60–62] This process is the one used for the commercial production of dichlorodifluoromethane. The catalyst is prepared by treating antimony trichloride with hydrogen fluoride and chlorine under pressure at 100°C. The composition of the product, which melts at 40°C., indicates that it is a mixture of SbF_2Cl_3 and SbF_3Cl_2 (14 to 20% fluorine); catalysts containing less fluorine give very uncertain results.[18,61] The introduction of chlorine into the reaction mixture along with the hydrogen fluoride during the course of the fluorination is necessary to insure that a part of the antimony is always in the pentavalent state; but it is also important that some of the antimony be left in the trivalent state (10 to 30%), since otherwise the vapor pressure of the catalyst becomes too high and it is volatilized. The amount of hydrogen fluoride added to the reaction mixture must be sufficient to maintain the proportion of fluorine in the catalyst at the desired level. In a few cases the reaction is quite vigorous at room temperature, but in general the best yields are obtained by working at 60° to 100°C. If it becomes necessary to carry out the fluorination at temperatures above 120°C., a pressure on the system of at least 2.7 atmospheres must be maintained in order to keep the contents in the liquid state. Phosphorus pentachloride has been used to replace the chlorine in this process.[57] When alkyl bromides are fluorinated, it is expedient to employ antimony tribromide and bromine in the reaction. The presence of water interferes with the fluorination.

A brief outline of the commercial process follows.[57] The alkyl chloride and hydrogen fluoride either separately or previously mixed enter the reaction vessel at the bottom and bubble up through the liquid catalyst. After they have emerged at the top, they pass into a scrubber containing the alkyl halide used in the process. Although the reaction is occasionally complete after one passage of the gases through the catalyst, usually it is necessary to recycle insufficiently fluorinated products. These compounds and any antimony compounds which have been volatilized are absorbed in the scrubber and returned to the reaction chamber. The pressure must be so regulated that the catalyst remains in the liquid state and that the products are gaseous. In certain cases a part of the alkyl fluoride which is formed is returned to the reaction vessel to be used as a solvent for the catalyst. Attached to the scrubber are absorption towers filled with water and with quicklime which remove the hydrogen halide from the gaseous mixture. Finally the products are passed through a drying tower containing concentrated sulfuric acid and are liquefied.

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[59] Kinetic Chemicals, Inc., U. S. Patent, 2,005,707.

[60] Kinetic Chemicals, Inc., U. S. Patents, 2,005,705, 2,005,708, 2,005,713; German Patent, 552,919; British Patent, 720,474; Henne, in *Organic Reactions*, Wiley, New York, 1944, Vol. II, p. 56.

[61] Kinetic Chemicals, Inc., U. S. Patent, 2,024,095.

[62] Kinetic Chemicals, Inc., French Patent, 46,349.

When a continuous process is not employed, the catalyst is prepared in the reaction vessel, the alkyl halide and hydrogen fluoride are passed in and allowed to react, and then the catalyst is regenerated with hydrogen fluoride and chlorine. The use of two sets of equipment is advantageous[18,62]; the reaction is then carried out either by preparing fresh catalyst in each one alternately or by connecting the two reaction vessels in series and starting the reaction in one and completing it in the second, using slightly different conditions in the two. In the first the temperature is maintained at 150° to 160°C. and a catalyst containing 10 to 20% fluorine and 3 to 10% trivalent antimony is employed; the temperature in the second is 145° to 155° and a catalyst containing 6 to 10% fluorine and 10 to 40% trivalent antimony is used. The pressures recommended for the process are 3 to 13.5 atmospheres. A similar process for the reaction of carbon tetrachloride with hydrogen fluoride in the presence of antimony chloride was patented earlier by I. G. Farbenindustrie.[63]

Only a few examples of these two methods can be mentioned here. Carbon tetrachloride reacts with hydrogen fluoride at 250°C. over a catalyst of charcoal and cupric chloride with the production of an 82% yield of trichlorofluoromethane and some dichlorodifluoromethane. The substitution of ferric chloride for the cupric chloride allows the reaction to be carried out at 150°C.; the yield of the trichlorofluoromethane is practically the same (88%). In a liquid phase process with an antimony catalyst at 60°, 36% of trichlorofluoromethane and 54% of dichlorodifluoromethane are produced from carbon tetrachloride. Over a charcoal catalyst chloroform produces 10% of dichlorodifluoromethane and 60% of dichlorofluoromethane at 300°, while over an antimony catalyst at 18° to 20° the percentage yields of the same two substances are 1 and 70%, respectively.

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[63] I. G. Farbenindustrie A.-G., British Patent, 370,356.

No attempt will be made to enumerate all the other reactions of this type which have been reported. Derivatives of the paraffin hydrocarbons from methane to butane, which contain any of the halogens in any proportions as well as unsaturated compounds such as ethylenic or allyl halides, can be fluorinated by the method outlined previously. In the latter case, however, saturation of the double bond occurs during the process.

That the compounds resulting from these reactions tend to lose hydrogen halides at higher temperatures is shown by the production of monochloro- and monofluoroethylene from ethylene chloride along with fluorochloroethane.[18] In order to keep such side reactions at a minimum, lower temperatures and pressures must be employed, and it is also advisable to use more chlorine in these reactions than is normally necessary. The excess chlorine is added to the unsaturated compounds and is partly replaced by fluorine. An example of a reaction of this kind is the production of difluoropentachloropropane from allyl iodide.

Hydrogen atoms are also frequently substituted by chlorine, as is shown by the formation of dichlorotetrafluoroethane and trichlorotrifluoroethane from trichloroethylene[18]; however, the replacement of all the hydrogen atoms does not always take place, because the reaction with tetrachloroethane gives trifluorodichloroethane.[18,60] Occasionally the substitution of a hydrogen atom takes place even when no free chlorine is present, a fact illustrated by the production of difluorohexachlorobutane from tetrabromobutane[57]; however, this can be avoided by using a catalyst containing more than 30% of trivalent antimony.[18]

The replacement of more halogen atoms by fluorine atoms is favored by an excess of hydrogen fluoride, by the presence of large quantities of catalyst, and by high temperatures. Hexachloroethane gives difluorotetrachloroethane at 100°C., but the main product at 150° is trifluorotrichloroethane.[57] The presence of oxygen atoms in the molecule does not appear to prevent the fluorination reaction, since tribromoacetyl fluoride affords fluorobromoacetyl fluoride,[57] and from chloropropyl alcohol a fluorochloro derivative containing no hydroxyl group is obtained.[57]

It was mentioned previously that the presence of water interferes with reactions in which fluid catalysts are used. A method for eliminating the moisture in hydrogen fluoride by mixing silicon tetrafluoride with it has been suggested in the patent literature.[64] The silicon fluoride should be an effective drying agent.

The fact that the reactions just described can be carried out just as successfully by continuous as by batch processes gives rise to the thought that they are not true catalytic processes and that the reagent which effects the fluorinations is not the hydrogen fluoride but the antimony compounds (by means of the mechanism outlined at the beginning of this section). Further evidence for this view-point is the fact that it was not possible to replace all 3 chlorine atoms on a trichloromethyl group by fluorine in any of the cases mentioned above. This behavior is particularly characteristic of the antimony chlorofluoride reagent (SbF_2Cl_3) first prepared and investigated by Swarts as a fluorinating agent.[65]

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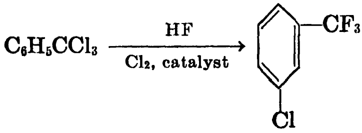
[64] General Motors Corporation, U. S. Patent, 1,973,069.

The complete fluorination of a trichloromethyl group by this method is possible in the case of aryltrichloromethyl and certain aliphatic compounds. Benzotrichloride and its derivatives can be transformed into the corresponding trifluorides by means of solid[34] as well as liquid catalysts[18,66]; even in these cases the chlorofluorides are also obtained. Nuclear halogen,

$$C_6H_5CCl_3 + 3HF \longrightarrow C_6H_5CF_3 + 3HCl$$

alkyl, or other trichloromethyl groups do not have an adverse effect on the reaction. Nuclear hydrogen atoms are substituted only when free chlorine is used in the replacement reaction; thus *m*-chlorobenzotrifluoride was produced from a reaction with benzotrichloride.[67]



The trichloromethyl group of 1,1,1,2-tetrachloroethane was completely fluorinated by heating the chloro compound at 160°C. under a suitable pressure with hydrogen fluoride and an antimony chlorofluoride catalyst

$$Cl_3CCH_2Cl \xrightarrow[\text{Catalyst}]{\text{HF}} F_3CCH_2Cl$$

containing only pentavalent antimony and 18% of fluorine. The yield of 1,1,1-trifluoro-2-chloroethane was 90%.[67]

B. In Absence of Catalysts

The replacement of the chlorine atoms in a trichloromethyl group can be effected by hydrogen fluoride just as easily without as with a catalyst. Several advantages can be gained by the elimination of antimony halides. The reactions are cleaner, since in the presence of catalysts considerable resinification and nuclear substitution often take place. Furthermore, such catalysts offer much greater difficulties toward recovery than does hydrogen fluoride.

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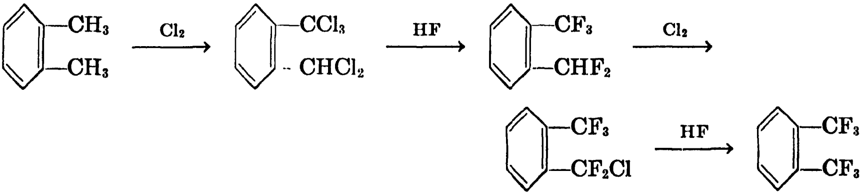
[65] Swarts, *Bull. soc. chim.*, 35, 1538 (1924).

[66] Kinetic Chemicals, Inc., U. S. Patent, 2,005,712.

[67] Kinetic Chemicals, Inc., U. S. Patent, 2,230,925.

A convenient laboratory method is that of Simons and Lewis,[68] which gives a yield of benzotrifluoride as high as 95% by passage of hydrogen fluoride into benzotrichloride at 0°C. Benzal chloride does not react under these conditions.[69] The industrial process may be effected by a method[70] similar to that just mentioned or by heating the components to 110° to 160°C. under a pressure of 10 to 14 atmospheres.[71,72] In the latter process the two reactants are added in stoichiometric quantities; the elimination of water, which would cause the hydrolysis of the benzotrichloride to benzoic acid, is essential. Nuclear halogen, alkyl, or carboxyl groups do not have any adverse effect on the reaction, but trichloromethylbenzonitrile cannot be fluorinated by this process.[69]

Benzene derivatives containing more than one trifluoromethyl group have been obtained in this way; however, the preparation of 1,2-bistrifluoromethylbenzene offered some difficulties, since the chlorination of *o*-xylene did not give the hexachloro compound. Instead, only 5 hydrogen atoms could be replaced by chlorine. Treatment of the pentafluoro-*o*-xylene with hydrogen fluoride produced the pentafluoro derivative, the remaining hydrogen atom of which could then be replaced by chlorine. A second reaction with hydrogen fluoride gave the desired compound. The behavior of pseudocumene and of durene was very similar.[73]



Attempts to prepare pentafluorophenylethane by heating pentachlorophenylethane and hydrogen fluoride at 145°C. under pressure were unsuccessful, since the last chlorine atom on the β-carbon atom could not be replaced. The product consisted of 1,1,1-trichloro-2,2-difluoro-2-phenylethane (29.8%) and 1,1,2,2-tetrafluoro-1-chloro-2-phenylethane (51.1%).[53]

$$C_6H_5CCl_2CCl_3 \xrightarrow{HF} C_6H_5CF_2CCl_3 + C_6H_5CF_2CF_2Cl$$

Application of the Swarts reaction gave no better results, and the use of the silver fluoride method afforded only small yields of the desired pentafluoro compound. A reaction between 1,1,1-trifluoro-2,2-dichlorophenylethane and hydrogen fluoride in the presence of antimony pentachloride likewise gave only a small amount of the pentafluoro derivative. The data gained from this problem showed that the resistance toward the replacement of chlorine atoms in pentachloroethane increases as the fluorine content increases, that the chlorine atom next to the phenyl group is substituted first, and that the last chlorine atom on the terminal carbon atom is extremely difficult to replace. On the other hand, if the terminal group is completely fluorinated first (by preparing trifluoroacetophenone[74] and treating it with phosphorus pentachloride), the remaining chlorine atoms are much easier to replace by fluorine; even hydrogen fluoride in the presence of antimony compounds is effective. Even in this case the adjacent fluorine atoms make the replacement of the chlorine atoms more difficult than those of benzotrichloride.

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[68] Simons and Lewis, *J. Am. Chem. Soc.*, 60, 492 (1938).

[69] Scherer, *Angew. Chem.*, 52, 457 (1939).

[70] Henne, in *Organic Reactions*, Wiley, New York, 1944, Vol. II, p. 62.

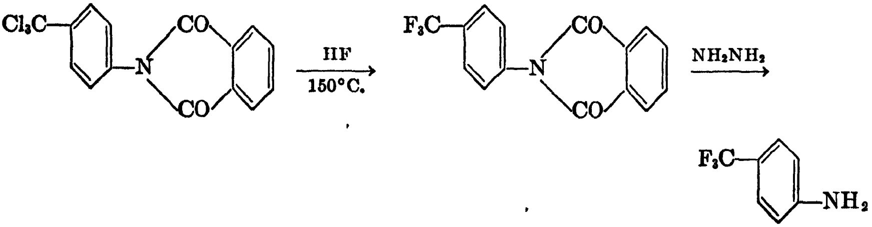
[71] I. G. Farbenindustrie A.-G., German Patent, 575,593.

[72] I. G. Farbenindustrie A.-G., French Patent, 745,293; Kinetic Chemicals, Inc., U. S. Patent, 1,967,244.

[73] I. G. Farbenindustrie A.-G., British Patent, 465,885; French Patent, 812,531; German Patent, 668,083.

$$C_6H_5COCF_3 \xrightarrow{PCl_5} C_6H_5CCl_2CF_3 \xrightarrow[\text{Catalyst}]{HF} C_6H_5CF_2CF_3$$

By protecting amino groups by imide formation with phthalic anhydride, it is possible to use this method for the production of aromatic amines with *o*- or *p*-trifluoromethyl groups (the meta derivatives are obtained in another way). The treatment of *N*-trichloromethylphenylphthalimide under a suitable pressure with hydrogen fluoride at 150°C. and removal of the phthalic acid residue by steam-distilling the product in the presence of hydrazine hydrate gives *p*-trifluoromethylaniline. It is essential that a small excess of hydrogen fluoride be used and that the reaction be effected in the liquid phase. If a solvent is necessary, methylene chloride may be employed. The yields usually are very good.[75]



A trichloromethyl group does not necessarily have to be attached to a phenyl group in order for this type of reaction to take place, since one attached to a sulfur atom will undergo fluorination. Trichloromethylphenyl sulfide is converted to the corresponding trifluoro derivative in a yield of 90% when it is heated with hydrogen fluoride to 50° to 100°C. under pressure. The product can be oxidized to the sulfone with chromic acid. Substituents in the benzene nucleus which do not interfere with the reaction are the following: —NO_2, —CF_3, —SCF_3, and —SO_2CF_3. The maintenance of anhydrous conditions is just as essential in this case as in those described above.[76]

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[74] Simons and Ramler, *J. Am. Chem. Soc.*, 65, 389 (1943).

[75] I. G. Farbenindustrie A.-G., British Patent, 459,890; French Patent, 805,704.

$$C_6H_5SCCl_3 \xrightarrow{HF} C_6H_5SCF_3 \xrightarrow{CrO_3} C_6H_5SO_2CF_3$$

Certain aliphatic trichloromethyl compounds of the type of 1,1,1-trichloroethane also can be fluorinated successfully with hydrogen fluoride alone by carrying out the reaction at elevated temperatures and pressures. The replacement of the chlorine takes place rapidly and completely under these conditions. Ethylidene chloride may be converted to the fluoride by the same method. The yields are lowered by the presence of moisture.[77]

$$CH_3CHCl_2 \xrightarrow{HF} CH_3CHF_2$$

The exchange reaction which proceeds most easily is that of the replacement of chlorine by fluorine in acid chlorides by hydrogen fluoride. A vigorous evolution of hydrogen chloride takes place when an acid chloride is added to liquid hydrogen fluoride.[78] Similar results are obtained with the acid bromides and iodides. The hydrogen chloride, being insoluble in hydrogen fluoride, volatilizes as it is formed. After the reaction is complete, the hydrogen fluoride is distilled, and the acid fluoride is dried over ignited potassium fluoride and is distilled. This method has been used for the preparation of the acid fluorides of the following acids: acetic, benzoic,[78] chloroacetic, *m*-bromobenzoic, *m*-nitrobenzoic, and phenylacetic.[14] The yields, which depended on the volatilities of the products, varied from 50 to 90%.

$$RCOCl + HF \longrightarrow RCOF + HCl$$

The replacement of chlorine atoms in both —CCl_3 and —COCl groups can take place simultaneously and the yields of the fluoro compounds should be good. The conversion of mono- and bistrichloromethylbenzoyl chlorides, their halogen derivatives, and the diacid chloride of trichloromethylbenzene-1,3-dicarboxylic acid into the corresponding fluoro compounds has been reported to take place with hydrogen fluoride at 50° to 150°C.[79]

3. Preparation of Fluorides from Amino Compounds

None of the methods discussed previously is suitable for the conversion of aromatic halides into fluorides, since the inertness of nuclear halogen atoms makes their replacement by hydrogen fluoride impossible. Up to the present time the decomposition of diazonium fluorides offers the only means of preparing aryl fluorides. The arylamine or its hydrochloride is dissolved in liquid anhydrous hydrogen fluoride, the solution of the amine hydrofluoride is cooled to 0° to 5°C., and the diazotization is effected with sodium nitrite or nitrous fumes. The solution of the diazonium fluoride is

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[76] I. G. Farbenindustrie A.-G., French Patent, 820,796.

[77] I. G. Farbenindustrie A.-G., German Patent, 670,130; French Patent, 798,421.

[78] K. Fredenhagen and Cadenbach, *Z. physik Chem.*, Abt. A, **164**, 201 (1933).

[79] I. G. Farbenindustrie A.-G., French Patent, 820,795.

$$C_6H_5NH_2 \xrightarrow[HF]{HNO_2} C_6H_5N_2F \xrightarrow{Heat} C_6H_5F + N_2$$

decomposed by warming it to 30° to 40°. After all the nitrogen has been evolved and the hydrogen fluoride has been distilled, the aryl fluoride is treated with dry potassium fluoride to remove any traces of hydrogen fluoride and water and is distilled.[80]

In this way fluorobenzene and *m*-fluorotoluene have been prepared from the corresponding amines in yields of 87 and 82%, respectively. Since 2 moles of water are formed in the reaction for every mole of amine diazotized, it is necessary to employ fairly large excesses of hydrogen fluoride. Since no *p*-aminoazobenzene, $H_2NC_6H_5N{=}NC_6H_5$, is formed under these conditions[14] an excess of sodium nitrite is recommended also.

A method involving the diazotization of amines in aqueous hydrofluoric acid has been discussed by Bockemüller.[81] One other reaction by means of which aryl fluorides have been obtained is that between a diazoamino compound and hydrogen fluoride.[82]

$$C_6H_5N{=}N{-}NHC_6H_5 \xrightarrow{HF} C_6H_5F + N_2 + C_6H_5NH_2$$

The preparation of alkyl and aralkyl fluorides by the diazo reaction has not been accomplished. Phenyldiazomethane reacted vigorously with hydrogen fluoride in ether solution and nitrogen was evolved, but only a little stilbene and no benzyl fluoride were obtained.[83] The products resulting from diazoheptane, by the same method, contained no fluorine. 1-Heptene but no tetradecene could be isolated from the reaction mixture.[84]

4. Preparation of Fluorides by Replacement of Hydroxyl and Certain Sulfur-Containing Groups

The substitution of an alcoholic hydroxyl group by a fluorine atom by means of the action of hydrogen fluoride has little value for preparative purposes. Meslans has shown that ethanol reacts with hydrogen fluoride under pressure at temperatures above 140°C., and at 190° the amount of ethyl fluoride formed is as high as 36%. The best yields are obtained at the optimum temperature of 210° to 220°. The hydrogen fluoride and ethanol must be used in a molar ratio of 4:1 in order to prevent the formation of ether. The propyl alcohols undergo the reaction in the same way.[85] It has been suggested that even wet hydrogen fluoride should react with alcohols, chloro alcohols, and polyhydroxy compounds at 100° to 250° in the absence of any catalytic substances, with the formation of fluorinated hydrocarbons.[32]

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[80] I. G. Farbenindustrie A.-G., German Patent, 600,706.

[81] Bockemüller, *Organische Fluorverbindungen*, Enke, Stuttgart, 1936, p. 55; Edwards, Ann Arbor, 1945.

[82] Klatt, *Z. anorg. allgem. Chem.*, **232**, 393 (1937).

[83] C.-L. Tseng, C.-H. Sze, and C. E. Sun, *J. Chinese Chem. Soc.*, **4**, 485 (1936); *Chem. Zentr.*, **1937,I**, 3789; *Chem. Abstracts*, **31**, 3903 (1937).

[84] C.-L. Tseng and T.-H. Ho, *J. Chinese Chem. Soc.*, **4**, 335 (1936); *Chem. Zentr.*, **1936,II**, 2894; *Chem. Absracts*, **31**, 1010 (1937).

According to Scherer the use of certain catalysts made possible the preparation of methyl and ethyl fluorides in good yields by means of reactions between the corresponding alcohols and hydrogen fluoride.[69] The formation of oxygen-free derivatives from chloropropyl alcohol by the action of hydrogen fluoride in the presence of chlorine and antimony chlorofluoride catalysts has already been mentioned.[61] Another patent has disclosed the use of beryllium difluoride for catalyzing reactions of this type and has shown that the hydrogen fluoride can be replaced by sodium bifluoride. An example of this reaction is the conversion of β,β'-dihydroxyethyl sulfide to the corresponding difluoro compound at 105°C.[86]

$$S(C_2H_4OH)_2 + 2NaHF_2 + 8BeF_2 \longrightarrow S(C_2H_4F)_2 + 2BeO \cdot 5BeF_2 + Na_2BeF_4 + 4HF$$

The work of Klatt[35,87] has shown that, just by being dissolved in liquid hydrogen fluoride, most hydroxy compounds form alkyl or acyl fluorides by the replacement of the hydroxyl group by a fluorine atom; at most the amounts formed are very small. In spite of this Klatt claimed to have isolated "quite considerable quantities of benzoyl fluoride" by shaking a solution of benzoic acid in hydrogen fluoride with petroleum ether; smaller amounts of the fluorides of cinnamic and salicylic acids were obtained. Further evidence for fluoride formation in these cases lies in the fact that the apparent concentration of the acids in hydrogen fluoride, as determined by conductivity measurements, is less than that obtained by ebullioscopic means. If the formation of an acid fluoride is assumed, the difference is

$$RCOOH + HF \rightleftharpoons RCOF + H_2O$$

easily explained by the fact that the acid fluoride formed still has the same effect as the acid on the boiling point but that its non-dissociation into ions lowers the conductivity of the solution. The same type of behavior is characteristic of alcohols but not of phenols, with which the apparent concentration determined by either method is the same. The quantity of the fluoride formed is by no means large enough in every case to be isolated; certain acyl and alkyl fluorides hydrolyze readily in hydrogen fluoride con-

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[85] Meslans, *Compt. rend.*, **115**, 1080 (1892); **117**, 853 (1894); *Ann. chim.*, **1**, 346 (1894).

[86] Societá Anonima Processi Privative Industriali, Italian Patent, 343,035; *Chem. Zentr.*, **1937**, **II**, 2432.

[87] Klatt, *Z. anorg. allgem. Chem.*, **222**, 289 (1935).

$$\mathrm{ROH + HF \rightleftharpoons RF + H_2O}$$

taining small amounts of water and in these cases the equilibrium is probably shifted toward the reversal of the reaction by the water formed.[88]

Hydrogen fluoride reacts with certain sulfur compounds, with the replacement of sulfhydryl groups or sulfur atoms by fluorine. Thioacetic acid when added to liquid hydrogen fluoride evolves hydrogen sulfide vigor-

$$\mathrm{CH_3COSH + HF \longrightarrow CH_3COF + H_2S}$$

ously, with the formation of acetyl fluoride. Thio alcohols and thiophenols do not react in this way.[81] Fluorochloromethane derivatives ($CFCl_3$, CF_2Cl_2, and CF_3Cl) can be obtained from reactions involving carbon disulfide, hydrogen fluoride, and halogens in the presence of catalysts such as antimony or heavy metal halides. The sulfur is evolved as hydrogen sulfide or, if larger quantities of hydrogen fluoride and chlorine are used, as sulfur dichloride. Similar reactions have been observed in the case of perchloromethyl sulfur chloride.[89]

IV. USE OF LIQUID HYDROGEN FLUORIDE AS SOLVENT

1. Solubility Characteristics of Organic Compounds

The solvent power of liquid hydrogen fluoride is unusually large and a wide variety of compounds is soluble in it. A list of substances which have been investigated is given by Fredenhagen.[88] As a general rule, liquid hydrogen fluoride dissolves all those substances which contain oxygen or sulfur in the molecule, probably by the formation of oxonium or sulfonium complexes. Basic compounds form salts. In all of these cases the addition complexes dissociate into complex organic cations and fluoride anions. In addition to these substances hydrogen fluoride dissolves a large number of other compounds, for which the process of solution is not completely understood. A characteristic property of hydrogen fluoride is that substances either are very soluble in it or are practically insoluble. A range of intermediate solubilities which is so important in the case of most other solvents is entirely absent in the case of liquid hydrogen fluoride.

The aliphatic hydrocarbons are practically insoluble, while the aromatic ones are soluble only to the extent of about 3% at 15°C.[90] The interesting observation has been made that the solubilities of the aromatic hydrocarbons can be increased markedly by the addition of a salt of a heavy metal such as the cyanide or azide of mercury or the azide or fluoride of silver. For every mole of the salt 4 moles of the hydrocarbon dissolve, probably by complex formation. On the other hand, the addition of such reagents does not affect the solubilities of aliphatic hydrocarbons and of biphenyl.[90]

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[88] K. Fredenhagen and Cadenbach, *Z. physik. Chem.*, Abt. A, **164**, 176 (1933).

[89] Imperial Chemical Industries, British Patent, 463,970; Kinetic Chemicals, Inc., U. S. Patent, 2,004,932.

[90] Klatt, *Z. anorg. allgem. Chem.*, **234**, 189 (1937).

The influence of substituents on the solubility of aromatic compounds is summarized by the following. If the parent compound has a group, such as a hydroxyl group, which is capable of adding hydrogen fluoride, negative substituents cause a decrease in the solubility. Thus phenols are very soluble, nitrophenols are only slightly soluble, and trinitrophenol is insoluble in hydrogen fluoride. Benzoic acid dissolves quite readily, while bromobenzoic acid is insoluble. If the parent compound has no active center, negative substituents having groups to which hydrogen fluoride adds increase the solubility. Benzene is not very soluble but nitrobenzene is very soluble. In those cases in which neither the parent compound nor the substituent has an active center, the solubility is always lowered by substitution. Thus, chloro- and bromobenzenes are quite insoluble in hydrogen fluoride.[81]

The explanation of the solubility characteristics of many compounds, such as the phthalic acids, however, is still obscure. *o*-Phthalic acid is very soluble in hydrogen fluoride, but isophthalic acid dissolves only to the extent of 3.5% at 19°C. and terephthalic acid is very insoluble. These differences are much greater in hydrogen fluoride than in water. All the biphenyl compounds studied were practically insoluble even though some had active groups (biphenyl, biphenylene oxide, biphenyl-*p*-sulfonic acid). Diphenyl ether showed the same behavior.[81,88]

2. Fluorination

The reactions of many organic compounds in the solid or liquid state are unusually violent with elementary fluorine, and in cases in which vapor phase fluorination is not possible, whether or not the reaction can be carried out depends on finding a suitable solvent which is indifferent toward fluorine. There are few solvents which fulfill this condition; carbon tetrachloride is attacked somewhat even at 0°C., and some chlorinated products are obtained along with the fluorinated ones.[91] The best solvents for the reaction are the commercial refrigerants, CCl_2F_2 and $C_2F_4Cl_2$, and liquid hydrogen fluoride, which cannot react with fluorine and which dissolve it readily.

[91] Bigelow, Pearson, Cook, and Miller, Jr., *J. Am. Chem. Soc.*, **55**, 4616 (1933); Henne, in *Organic Reactions*, Wiley, New York, 1944, Vol. II, p. 69.

A process has been described by du Pont in which the substance to be fluorinated is dissolved or suspended in hydrogen fluoride, and fluorine is introduced into the mixture.[92] When very sensitive substances are involved, it is best to add the fluorine dropwise as a solution in hydrogen fluoride. The temperature at which the reaction mixture is maintained depends on the particular compounds involved (−70° to 70°C.), and a pressure great enough to keep the products in the liquid state is applied. Catalysts such as iodine, antimony, and heavy metal halides may be added in proportions of 0.1 to 5%. Aliphatic hydrocarbons, ethers, and even compounds such as divinylacetylene have been fluorinated by this method. In the aromatic series the reaction has been applied to hydrocarbons, their halogen, nitro, and amino derivatives, carboxylic and sulfonic acids, pyridine, quinoline, anthraquinone, benzanthrone, indigo and its derivatives, brilliant yellow, rhodamine blue, and the phthalocyanines. Up to 7 atoms of fluorine per mole have been introduced into various phthalocyanines and their heavy metal salts.[93]

The presence of small quantities of water interferes with the reaction, since it leads to the formation of ozone and the subsequent oxidation of the organic materials.

3. Nitration and Sulfonation

The nitration of benzene was effected by Simons and co-workers by treating benzene with a solution of nitric acid (100%) in liquid hydrogen fluoride at 0°C. The yield of nitrobenzene was 83%; no dinitrobenzene was formed and the treatment of nitrobenzene by the same process gave no dinitrobenzene.[94] These reactions were not very easy to carry out since pure, anhydrous nitric acid is quite difficult to prepare and since it reacts with hydrogen fluoride with some violence (the mixture becomes warm, spatters, and evolves nitrous fumes).

A simpler process by which the nitration reactions can be effected by solutions of potassium nitrate in liquid hydrogen fluoride had been recommended previously by Fredenhagen.[95] Molecular weight determinations and conductivity measurements have shown conclusively that potassium nitrate dissolved in hydrogen fluoride undergoes a reaction as follows[15]:

$$KNO_3 + 2HF \longrightarrow (HNO_3{\cdot}H)^+ + K^+ + 2F^-$$

This nitrating mixture is essentially the same and is equivalent to that used by Simons, since nitric acid probably reacts with hydrogen fluoride with the formation of the same complex cation. Evidently the presence of potassium ions in the solution does not reverse the reaction. This reagent has the advantage that in its preparation only a mild heating effect is noted. Since this method has not been described elsewhere, two examples are given here to illustrate it.[14]

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[92] E. I. du Pont de Nemours, French Patent, 761,946; U. S. Patent, 2,013,030.

[93] E. I. du Pont de Nemours, U. S. Patent, 2,227,628.

[94] Simons. Passino. and Archer, *J. Am. Chem. Soc.*, **63**, 608 (1941).

[95] K. Fredenhagen, German Patent, 529,538.

1. Nitration of Benzoic Acid. To a solution of 15 g. of benzoic acid in 50 g. of liquid hydrogen fluoride contained in a platinum flask which is cooled in an ice bath is added a solution of 13 g. of potassium nitrate in 50 g. of liquid hydrogen fluoride. The reaction mixture is allowed to stand in ice for 30 minutes during which time it is shaken occasionally. The hydrogen fluoride is removed by heating the flask to 40°C. and by passing dry air through it, or it is distilled if the recovery of it is desired. The residue, which is a mixture of *o*- and *m*-nitrobenzoic acids, is dissolved in 2 *N* aqueous potassium carbonate or potassium hydroxide; the solution is filtered from potassium fluoride if necessary, and is acidified with dilute sulfuric acid. The acids are extracted with ether and the ethereal extract is treated with diazomethane. Evaporation of the ether leaves a thick yellow syrup, from which methyl *m*-nitrobenzoate slowly crystallizes in dense colorless prisms. The solid is filtered and washed with a little cold methanol, and the washings are added to the filtrate, which is allowed to stand while further crystallization takes place. The combined fractions are recrystallized from methanol, after which the ester melts at 79.8°C. The combined filtrates contain the ortho ester, which is purified by distillation at 141° to 143°C. at 6 mm.

Saponification of the meta ester in aqueous or alcoholic solution gives the free acid in a 59 to 61% yield. The ortho ester is saponified by barium hydroxide in methanol, and the free acid is crystallized from water. The yield is 25 to 30%.

2. Nitration of Aniline. To 100 g. of liquid hydrogen fluoride are added gradually 15 g. of aniline nitrate in pellet form, care being taken that each portion reacts completely before the next pellet is added. A slight crackling noise indicates the end of the reaction. After all the amine salt has been added, the reaction mixture is shaken occasionally and allowed to stand in an ice bath for 30 minutes. The hydrogen fluoride is removed, and the residual dark green solution is poured into a large volume of ice water. The hydrolysis of the 4-nitroaniline hydrofluoride, which is quite extensive in aqueous solution, is completed by the addition of magnesium carbonate; this treatment does not affect the salt of the 3-nitroaniline, which remains in solution. The 4-nitro derivative is extracted by ether, purified by vacuum sublimation at 150° to 170°C. at 7 mm., and crystallized from toluene. It melts at 146.3°C., and its acetyl derivative melts at 213°C. The aqueous solution is made alkaline and the 3-nitro deriva-

tive is extracted by ether. Crystallization from water affords a product melting at 113.7°C. The acetyl derivative melts at 152.4°C.

All basic compounds are nitrated simply by dissolving their nitrates in liquid hydrogen fluoride. The reaction can also be carried out in heterogeneous systems, so that hydrocarbons, which are either very slightly soluble or insoluble in hydrogen fluoride, can be nitrated. It is recommended that in these cases the mixture be stirred or agitated on a shaking machine for several hours. In homogeneous systems the reaction proceeds very rapidly at 0°C. upon mixing of the components and is complete in a few minutes. Because of the low boiling point of hydrogen fluoride it would not be possible for a nitration reaction, which is strongly exothermic, to become heated above 30°C. As yet no reaction which shows such a strong heating effect has been observed.

In the accompanying table are listed the substances which have been investigated thus far. The nitrations were effected with equimolecular quantities of potassium nitrate in hydrogen fluoride.

Nitrations Effected by Potassium Nitrate in Hydrogen Fluoride

Compound nitrated	Product	Yield, %
Phenol	*o*-Nitrophenol	41
	p-Nitrophenol	47
o-Cresol	*o*-Nitrocresol	18
α-Naphthol	Nitronaphthol	20
Guanidine	Nitroguanidine	83
Urethan	Nitrourethan	52
Acetanilide	*p*-Nitroacetanilide	75
Benzaldehyde	*o*-Nitrobenzaldehyde	28
	m-Nitrobenzaldehyde	50
Diethyl terephthalate	Diethyl 2-nitroterephthalate	52
Anthraquinone	Dinitroanthraquinone	35
Phenanthraquinone	2-Nitrophenanthraquinone	58
	4-Nitrophenanthraquinone	16
Fluorenone	2-Nitrofluorenone	30
	Dinitrofluorenone	47
Quinoline	Nitroquinoline	74
Benzene	Nitrobenzene	75
Nitrobenzene	*m*-Dinitrobenzene	55
Toluene	*o*- and *p*-Nitrotoluene	20
	Dinitrotoluene	10
o-Xylene	Nitroxylene	21
p-Xylene	2,3- and 2,6-dinitroxylene	27
Naphthalene	Nitronaphthalene	6
	1,5-Dinitronaphthalene	30
Tetralin	1,3-Dinitrotetralin	30
Decalin	Nitrodecalin	11

As yet it has not been possible to formulate any rules regarding the position of substitution. It should be mentioned that in a few cases the nitration reactions were accompanied by oxidation or resinification of the organic materials. Examples of compounds with which this occurred are anthracene, alizarin, and methylcyclohexane. The only substance which could not be nitrated under these conditions is pyridine.

Sulfonations were carried out by Simons by procedures similar to those used for nitrations. Concentrated sulfuric acid was dissolved in liquid hydrogen fluoride, and the compound to be sulfonated was heated with the solution in an autoclave. The ratio of sulfonic acid to sulfone in the products depended on the temperature at which the reaction was effected. At 85° to 90°C. benzene gave a 75% yield of benzenesulfonic acid and less than 1% of diphenylsulfone, while a 40% yield of the sulfone was obtained when the reaction was carried out at 140° to 150°. Unsymmetrical sulfones can be prepared by allowing a hydrocarbon to react with a sulfonyl chloride in solution in hydrogen fluoride.[94]

$$C_6H_6 + H_2SO_4 \xrightarrow{HF} C_6H_5SO_3H + H_2O$$

$$C_6H_5SO_3H + C_6H_6 \xrightarrow{HF} C_6H_5SO_2C_6H_5 + H_2O$$

The objections pointed out above to the use of anhydrous nitric acid in hydrogen fluoride apply here also. Concentrated sulfuric acid and hydrogen fluoride react with each other very violently with the formation of fluorosulfonic acid. This compound which is probably the active sulfonating reagent is present in solutions of potassium sulfate in hydrogen fluoride.[23] Thus, such solutions can be used for sulfonations in the same way in which solutions of potassium nitrate in hydrogen fluoride are employed for nitrations.

Higher temperatures than those necessary for the nitration of a compound must be used for its sulfonation. The nitration of benzene and the rearrangement of aniline nitrate into nitroaniline take place smoothly at 0°C., but the sulfonation of benzene must be effected under pressure at 100° and the rearrangement of aniline sulfate into sulfanilic acid requires refluxing of the hydrogen fluoride solution of the salt.[14] The yields generally are quite satisfactory.

4. Molecular Rearrangements

Several rearrangements ordinarily effected by other reagents have been shown to take place with hydrogen fluoride. The alkylation of phenol by *tert*-butylbenzene was carried out at 0°C. in the presence of hydrogen fluoride with the production of 10% of *p*-*tert*-butylphenol[96]; the reaction was not investigated at higher temperatures, but it is probable that the yield of butylphenol would be increased. The Beckmann rearrangement of benzophenone oxime in acetic acid or ether solutions of hydrogen fluoride gave a 72% yield of benzanilide.[96]

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[94] Simons Archer, and Randall, *J. Am. Chem. Soc.*, **62**, 485 (1940).

The Fries rearrangement of phenyl acetate in pentane solution did not take place in the presence of hydrogen fluoride at room temperature, but under pressure at 100°C. *p*-hydroxyacetophenone was formed in a 33% yield.[96] Experiments on the preparation of hydroquinone monobenzoate from hydroquinone and benzoic acid in liquid hydrogen fluoride led Fieser and Hershberg to the conclusion that the Fries rearrangement did not take place to any appreciable extent at low temperatures,[97] but further work with a number of phenol esters has shown that the reaction can be effected ordinarily by refluxing a solution of the ester in liquid hydrogen fluoride (about 25°C.), and that the rearrangement of phenyl acetate takes place at 0°C.[14] The yields of hydroxy ketones obtained from a few esters by this method are as follows: phenyl acetate (*p*-hydroxyacetophenone 92%), phenyl benzoate (*p*-hydroxybenzophenone 95%), phenyl salicylate (2,4′-dihydroxybenzophenone 40%). This method of effecting the Fries rearrangement did not appear to lead to the production of the ortho derivatives to the same extent as other methods. The yields decreased markedly when water was present because of the hydrolysis of the esters. The same hydroxy ketones were formed by refluxing solutions of phenol and the corresponding acid chlorides in hydrogen fluoride.

The rearrangement of *p*-cresyl benzenesulfonate to 2-hydroxy-4-methyldiphenylsulfone was effected by Simons by a method similar to that which he used for the Fries rearrangement. The reaction took place under pressure at 100°C. to the extent of 10% (*cf.* the rearrangement reaction catalyzed by aluminum or zinc chloride in nitrobenzene solution).[98]

The possibility of rearrangements which are reversible under certain conditions must always be kept in mind whenever physical measurements such as ebullioscopic molecular weight determinations are made on organic compounds dissolved in hydrogen fluoride. An example of this is the keto-enol isomerism exhibited by resorcinol and phloroglucinol in hydrogen fluoride.[23]

V. DEGRADATIVE REACTIONS EFFECTED BY HYDROGEN FLUORIDE

1. Alkyl Halides

During the course of their reaction with hydrogen fluoride the halides of the paraffin hydrocarbons not only suffer replacement of their halogen atoms by fluorine atoms but also occasionally lose hydrogen halides with the formation of olefins. The loss of the hydrohalogen acid is usually due to the high temperatures involved in the replacement reaction and is not connected with the presence of hydrogen fluoride; but there are a few cases in which hydrogen fluoride does exert a catalytic effect.

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[97] L. F. Fieser and Hershberg, *J. Am. Chem. Soc.*, 61, 1272 (1939).
[98] Chemische Fabrik von Heyden A.-G., German Patent, 532,403.

An example of a similar reaction which involves the loss of chlorine rather than hydrogen chloride is the production of dichlorostilbene from diphenyltetrachloroethane in the presence of hydrogen fluoride at 100°C.[55]; no reaction occurs when copper powder is used as the catalyst until the temperature is raised above 160°C.[99]

In a study of the action of hydrogen fluoride on tertiary alkyl halides Simons made the unexpected observation that *tert*-amyl chloride rearranged in liquid hydrogen fluoride at 0°C. with evolution of hydrogen chloride and the production of *tert*-butyl chloride. In addition to the *tert*-butyl chloride small quantities of hexyl, heptyl, decyl or undecyl (possibly both), and pentadecyl chlorides were also isolated. All the products were free from fluorine.[100]

2. Derivatives of Acids

The cleavage of acid anhydrides by hydrogen fluoride with the production of the corresponding acid fluorides is a reaction of some preparative importance. This type of reaction was first carried out by Colson, who

$$(RCO)_2O + HF \longrightarrow RCOF + RCOOH$$

prepared acetyl and propionyl fluorides by dissolving hydrogen fluoride in the corresponding anhydrides.[101,102] A method which consisted of dissolving the anhydride in liquid hydrogen fluoride, in which the reaction took place instantaneously, and working up the product in the usual way was used by Fredenhagen for the preparation of the fluorides of acetic, chloroacetic, and benzoic acids.[88] Except in those cases in which the synthesis of an acid anhydride is easier than that of the acid chloride, this method offers no particular advantage over that in which the acid chlorides are used. Cyclic anhydrides such as those of phthalic and maleic acids do not react with hydrogen fluoride.[87]

No reaction takes place between acid amides and nitriles and hydrogen fluoride.[14]

The cleavage of esters does not take place when strictly anhydrous hydrogen fluoride is used, but if traces of water are present hydrolysis of the esters proceeds very easily. This accounts for the dependence of the yield in the Fries reaction on the water content of the hydrogen fluoride used. According to Fredenhagen[88,103] alkyl, acyl, and hexosyl fluorides in hydrogen fluoride solutions are hydrolyzed very easily by small amounts of water, and similar observations were made by Klatt[35] and Simons[104] in work with ethyl fluoride and ethyl acetate.

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[99] Onufrowicz, *Ber.*, **17**, 835 (1884).

[100] Simons, Fleming, Whitmore, and Bissinger, *J. Am. Chem. Soc.*, **60**, 2267 (1938).

[101] Colson, *Compt. rend.*, **122**, 243 (1896).

[102] Colson, *Bull. soc. chim.*, **17**, 59 (1897).

Hydrogen fluoride reacts with sugar acetates easily, with the replacement of one acetyl group by a fluorine atom in yields between 30 and 70%. An example of such a reaction is the formation of fluorotriacetyl-L-arabinose from tetraacetyl-L-arabinose in a 65% yield.[105] The fluoroacetylhexoses thus obtained can be converted into the hexosyl fluorides in good yields by treatment with sodium methoxide. Glucosyl fluoride is obtained in a yield of 84% from fluorotetraacetylglucose in this way.[106]

3. Glucosides

Attempts to effect the cleavage of ethers by hydrogen fluoride have been most unsuccessful. Practically all of the aliphatic and aromatic ethers studied up to the present time were recovered unchanged after prolonged refluxing with hydrogen fluoride.[23] The only exception was diphenyl ether, from which some phenol could be isolated after it had been heated to 210°C. with hydrogen fluoride.[104] The thio ethers were just as inert to the action of hydrogen fluoride,[81] but the glucoside type of ether linkage did not show this inertness.

Fredenhagen[52,103] discovered that a large quantity of cellulose dissolves instantly in hydrogen fluoride, and that under suitable conditions a nearly quantitative yield of glucose can be isolated from such solutions. The transformation of the cellulose into glucosyl fluoride, which takes place immediately, is indicated in the following equation:

$$(C_6H_{10}O_5)_x + x\mathrm{HF} \longrightarrow x\mathrm{C_6H_{11}O_5F}$$

Proof of this is found in the fact that the electrical conductivity and the boiling point elevation of solutions of cellulose in hydrogen fluoride are practically identical with those of glucosyl fluoride solutions of equivalent concentration. Furthermore, when the utmost precautions for the elimination of water from the reactants are observed, glucosyl fluoride can be isolated.

If the hydrogen fluoride is eliminated from the cellulose solutions by distillation or evaporation in a current of air, neither glucose nor glucosyl

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[103] K. Fredenhagen and Cadenbach, *Angew. Chem.*, 46, 113 (1933).

[104] Simons and Archer, *J. Am. Chem. Soc.*, 62, 1623 (1940).

[105] Brauns, *J. Am. Chem. Soc.*, 45, 833, 2381 (1923); 46, 1484 (1924); 48, 2776 (1926); 49, 3170 (1927); 51, 1820 (1929).

[106] Helferich, Bäuerlein, and Wiegand, *Ann.*, 447, 30 (1926); Helferich and Gootz, *Ber.*, 62, 2505 (1929).

fluoride is obtained, but the residue is a fluorine-free substance of high molecular weight called *polyglucosan.* It has reducing properties which are somewhat variable. The formation of this polymeric substance is due to the fact that fluorides in solution in hydrogen fluoride are unusually sensitive to traces of water; thus the glucosyl fluoride is hydrolyzed by traces of moisture present in the reaction mixture and the glucose formed condenses to produce polyglucosan as the hydrogen fluoride is removed from the solution. The products resulting from the evaporation of the solvent from solutions of glucose in hydrogen fluoride are very similar to those obtained from cellulose.[107]

Helferich was unable to isolate any glucosyl fluoride from the solution of cellulose in hydrogen fluoride,[108] but his work was carried out at a time when the preparation of strictly anhydrous hydrogen fluoride had not yet been accomplished, and the technique for handling it had not been completely developed. He reported that the addition of water to the solutions of cellulose within 5 minutes after they were made gave a precipitate, a fact which indicates the use of non-anhydrous hydrogen fluoride. Furthermore, his method of drying the cotton wads and of adding them to the acid did not insure the exclusion of moisture. In the preparation of glucosyl fluoride it is necessary for the cotton to be dried in the reaction flask and for the hydrogen fluoride to be distilled into the vessel. Elaborate precautions for the exclusion of moisture must be observed in order for the reaction to proceed properly.

A study of the water-soluble, fluorine-free polyglucosan was undertaken by Helferich, who called it *cellan.* This weakly reducing substance can be purified as its acetyl derivative. It resembles the dextrins in its greater solubility in cold than in warm pyridine. It consists only of glucose units, but the connecting links between the units do not always involve the same hydroxyl group. The analysis of cellan and its acetyl derivative, its rotation of polarized light, and its solubility agreed so well with those of the products obtained by the action of hydrogen fluoride on glucose and cellobiose that Helferich also came to the conclusion that cellan was formed by the condensation of the glucose or glucosyl fluoride which resulted from the degradation of the cellulose. In an analogous way *amylan,* a substance very similar to cellan, was obtained from starch. Another interesting observation made by Helferich in this work was the fact that both α- and β-glucose as well as glucosides dissolved in hydrogen fluoride show the same specific rotation; this would indicate a conversion of the α into the β form.[108]

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[107] K. Fredenhagen and Helferich, German Patent, 521,340.

[108] Helferich and Böttger, *Ann.,* 476, 150 (1929); Helferich, Stärker, and Peters, *ibid.,* 482, 183 (1930); Helferich and Peters, *ibid.,* 494, 101 (1932).

4. Wood Sugar Process

It was inevitable that the action of hydrogen fluoride on cellulose should become the basis for a new process for making sugar from wood. Both liquid and gas phase processes have been developed and both require predrying of the wood. A water content up to 2% can be tolerated in the reaction mixture, but as the water content increases from that point the decomposition reaction slows down. The processes described below are not necessarily confined to the use of wood as a raw material; sugar can be made also from other materials such as straw, reeds, and potato plants.

The liquid phase process requires that the amount of liquid hydrogen fluoride used at least be equal to the weight of wood to be treated. After the reaction has been completed, the solution of wood sugar in hydrogen fluoride is decanted and the acid is evaporated. The decomposed wood is extracted with water, and the sugar solution is neutralized with calcium carbonate, filtered, and concentrated under diminished pressure. The weight of sugar obtained is equal to 65% of the weight of dry wood used; the rest of the product consists chiefly of lignin contaminated with small amounts of pentosans and acetic acid.[109]

When the decomposition is carried out in the gas phase, a liquid reaction zone is formed by adsorption of hydrogen fluoride on the surface of the wood.[110] This process is exothermic, but the reaction mixture cannot become superheated, because as the temperature rises the adsorption of hydrogen fluoride diminishes. This causes the reaction to proceed at a slower rate and the temperature drops. After the decomposition is completed, the hydrogen fluoride is removed by heating the reaction mixture or by aerating it. The reagent is then circulated over a fresh charge of wood or is recovered by adsorption over an alkali fluoride. The product is worked up by the method just described.

According to Mayrhofer, Bohunek, and Hoch, the wood particles react rapidly on the surface, but the shrinking which takes place simultaneously with this reaction causes the surface to become covered with a protective layer, which makes the penetration of hydrogen fluoride into the interior of the wood particles very difficult.[111] Air retained by the wood cells presents a similar barrier to the penetration of the gas, and necessitates the use of vacuum equipment for its removal. The use of diminished pressures also facilitates the removal of the last traces of moisture from the wood, which is introduced into the reaction vessel directly from the drying ovens while it is still warm. The gaseous process requires a remarkably small amount of hydrogen fluoride; if the quantity of the acid is reduced below a certain minimum value, however, a treatment of the product with dilute mineral acids becomes necessary for the completion of the degradation. The treatment of 500 g. of wood with 360 g. of 96% hydrogen fluoride gives 250 g. of a water-soluble product having 19.3% of the reductive power of glucose. The use of 50 g. of hydrogen fluoride gives a product which requires further treatment with dilute acids, and the yield of wood sugar is only 200 g. Thus the yields are smaller than those obtainable by the Fredenhagen liquid phase process. The fact that the liquid phase process requires more hydrogen fluoride is no particular disadvantage, since the acid can easily be recovered almost quantitatively.

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[109] K. Fredenhagen and Helferich, Canadian Patent, 286,179; U. S. Patents, 1,883,676–7.

[110] I. G. Farbenindustrie A.-G., French Patent, 711,393; Swedish Patent, 70,253; German Patents, 560,535, 585,318, 606,009.

[111] Mayrhofer, Bohunek, and Hoch, Austrian Patents, 147,494, 151,241; Lüers, *Holz Roh-u. Werkstoff*, 1, 342 (1938).

Since the decomposition of wood can be carried out on a small scale quickly and easily and the lignin is not dissolved in the process, a new method for the quantitative determination of lignin has been based on this reaction.[112] The same process is an excellent one for the preparation of lignin.[113]

VI. USE OF HYDROGEN FLUORIDE FOR CATALYSIS OF ORGANIC REACTIONS

1. Polymerization

Although many unsaturated compounds add hydrogen fluoride (see Section III, 1 and 2), others which do not add the gas so readily are polymerized for the most part by it. Even those which add hydrogen fluoride may undergo polymerization as the primary reaction under certain conditions. A few examples of compounds which polymerize easily are the following: amylene, butadiene, isoprene, dipentene, styrene, indene, pyrrole, thiophene, thionaphthene, and piperylene.[88] Usually the reaction proceeds very rapidly and leads to products of very high molecular weights; products of a lower degree of polymerization are obtained only if the reaction is effected in solution. Styrene gives a very brittle, bright yellow polymer immediately on being added to liquid hydrogen fluoride, but when it is dissolved in benzene and hydrogen fluoride is added to the solution cooled to −10°C., a white plastic substance is obtained.[114] The use of pressures above atmospheric occasionally increases the tendency of some substances to polymerize, and the use of other catalysts (boron fluoride, heavy metal halides)[115] in connection with hydrogen fluoride is recommended for the preparation of polycumarone resins.

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[112] Wiechert, *Cellulosechemie*, **18**, 57 (1940); Klatt, *Angew. Chem.*, **48**, 112 (1935).

[113] Wiechert, *Papierfabrikant*, **37**, 325, 339 (1939).

[114] K. Fredenhagen, German Patent, 524,220.

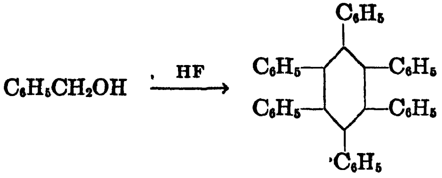
[115] F. Hofmann and Stegemann, German Patent, 492,345. See the chapter by Kästner on boron fluoride (pages 264 *et seq.*).

The treatment of unsaturated fats and vegetable oils with hydrogen fluoride gives products similar to those obtained by the thermal polymerization of those substances. Materials with properties which make them suitable for use as rubber substitutes are formed by the action of liquid hydrogen fluoride on poppy seed oil, castor oil, linseed oil, and wood tar oils. By passing gaseous hydrogen fluoride into linseed oil at 20° to 40°C. a lithographic oil is obtained.[116]

The behavior of rubber is very interesting; when it is added to liquid hydrogen fluoride, it swells to a very large extent, becomes hard and brittle, and finally takes on a yellow color.[117] The product contains 1.5 to 2.5 atoms of fluorine per isoprene unit and has an iodine number of 75, one-fifth that of the starting material. Since the substance is thermoplastic, it can be worked into varnishes stable toward acid and alkali; it gives films very similar to those of unplasticized nitrocellulose. If the polymerization is carried out in solutions of rubber in *p*-cymene or benzene, a white powder is formed which is readily soluble in gasoline, benzene, and the chlorinated hydrocarbons.[118] The polymerization of rubber by aqueous hydrofluoric acid (50 to 85%) at temperatures of from 40° to 100°C. has been reported to produce substances with leather-like properties.[119]

According to Grosse and Linn all the alkyl fluorides except ethyl fluoride are polymerized by prolonged contact with hydrogen fluoride at room temperature.[17] Products are obtained which are similar to those produced from the corresponding olefins. In Wiechert's studies, however, alkyl fluorides could be recovered unchanged from hydrogen fluoride.[14]

Benzyl alcohol and saligenin are resinified in liquid hydrogen fluoride with the production of fluorine-free products.[35] According to Calcott,



benzyl alcohol gives 1,2,3,4,5,6-hexaphenylcyclohexane.[120] Prolonged refluxing of solutions of acetaldehyde, acetone, and furfural in hydrogen fluoride produces condensation products.[1,23] Klatt thought mesitylene was formed from the polymerization of acetone,[121] but Simons obtained only inseparable mixtures of polymers.[1] Acetone can be recovered unchanged from hydrogen fluoride solutions which have not been heated above room temperature.[121]

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[116] K. Fredenhagen, German Patent, 551,787.
[117] Staerker, Thesis, Greifswald (1930).
[118] B. F. Goodrich Co., U. S. Patent, 2,168,279.
[119] I. G. Farbenindustrie A.-G., U. S. Patent, 2,187,185.
[120] Calcott, Tinker, and Weinmayr, *J. Am. Chem. Soc.*, 61, 1010 (1939).
[121] Klatt, *Z. physik. Chem.*, Abt. A, 173, 115 (1935).

The number of unsaturated compounds which may be polymerized by hydrogen fluoride is limited by the fact that those substances with an oxygen atom in the immediate vicinity of the center of unsaturation are not affected by hydrogen fluoride. Examples of such compounds are allyl alcohol and cinnamic acid, which form oxonium salts with hydrogen fluoride.[35]

2. Formation of Esters and Ethers

Only small yields of esters are obtained from the reactions of alcohols and acids in hydrogen fluoride (ethyl acetate[31] 17.5%, hydroquinone monobenzoate[97] 9%). The poor yields are due to the fact that the equilibrium in hydrogen fluoride solutions favors the left-hand side of the equation. The easy hydrolysis of esters by traces of water in hydrogen fluoride confirms this fact.

$$\mathrm{ROH + R'COOH \overset{HF}{\rightleftharpoons} R'COOR + H_2O}$$

On the other hand, hydrogen fluoride favors the formation of phenyl esters from phenol and acid chlorides; phenol and benzoyl chloride dissolved in hydrogen fluoride at 0°C. give a 90% yield of phenyl benzoate. In these reactions, however, the possibility of the occurrence of a Fries rearrangement must be considered; phenol and acetyl chloride react at 0°C. with the formation of 20% of phenyl acetate and 46% of *p*-hydroxyacetophenone.[14]

Good yields of esters have been obtained by the addition of acids to olefins in liquid hydrogen fluoride at 0°C. The reaction of cyclohexene

$$\mathrm{RCH{=}CH_2 + R'COOH \xrightarrow{HF} R'COOCH_2CH_2R}$$

with butyric or acetic acids gave 70% of the corresponding esters, while esterification of acetic and butyric acids by octene afforded the esters in 29 and 47% yields, respectively. In the latter cases considerable polymerization took place simultaneously with the esterification reaction. Attempts to esterify acetic acid by trimethylethylene gave polymeric products only.[31]

Attempts to prepare ethers by the condensation of an alcohol with an olefin in hydrogen fluoride gave very poor results. A reaction with cyclo-

$$\mathrm{RCH{=}CH_2 + R'OH \longrightarrow RCH_2CH_2OR'}$$

hexene and cyclohexanol gave a 12% yield of dicyclohexyl ether, but the main product of the reaction was cyclohexyl fluoride (61.5%), formed by the addition of hydrogen fluoride to cyclohexene. No ether was obtained from cyclohexene and isopropyl alcohol, but the product contained 3.5%

of dicyclohexyl ether and 2% of cyclohexanol. Similarly no ether could be isolated from the reaction between propylene and ethanol.[31]

The condensation between phenol and methanol in hydrogen fluoride gave a good yield of anisole, but all attempts to prepare phenetole by a similar reaction failed. Instead, ethylphenol was formed. The formation of diphenyl ether by heating phenol with hydrogen fluoride under pressure to 200°C. could not be accomplished.[122]

3. Acylation

The acylation of phenol and toluene by acids, acid anhydrides, acid chlorides, and esters has been studied by Simons.[123] The yields obtained by the use of these reagents are indicated in parentheses after the following equations:

$$\text{R—H} + \text{R'COOH} \longrightarrow \text{RCOR'} + \text{H}_2\text{O (31 to 55\%)} \qquad (1)$$

$$\text{R—H} + (\text{R'CO})_2\text{O} \longrightarrow \text{RCOR'} + \text{R'COOH (27\%)} \qquad (2)$$

$$\text{R—H} + \text{R'COCl} \longrightarrow \text{RCOR'} + \text{HCl (13 to 45\%)} \qquad (3)$$

$$\text{R—H} + \text{R'COOR''} \longrightarrow \text{R—R'' (chiefly)} + \text{RCOR' (trace)} + \text{H}_2\text{O} \qquad (4)$$

The acid formed in the second reaction can produce more of the ketone by reacting with the aromatic compound. These reactions were effected under pressure at 100°C. with the compound to be acylated present in excess; the use of rather large quantities of hydrogen fluoride was necessary. In the case of toluene the acyl group entered the para position. Small quantities of diacyl derivatives were obtained also.

When hydrogen fluoride is used as the condensing agent, the free acids afford better yields than the acid chlorides; the reverse is true for aluminum chloride. However, Fieser found that the acylation of acenaphthene by either acetic acid or acetyl chloride gave the same yields and the same proportion of isomers.[124] The anhydrides give no better yields than the free acids,[97] a fact which makes it appear unlikely that the acylation takes place via intermediate acid fluorides formed from the acids or their derivatives.

The acylation of acenaphthene was studied extensively by Fieser. The reaction with acetic acid gave a 25% yield of 1-acetoacenaphthene, but only the 3-isomers were formed in condensations with benzoic (62 to 70%) and succinic acids (53%).

By working under pressures up to 4 atmospheres, the yield of 1-acetoacenaphthene (I) could be raised to 37%; the 3-isomer (II) was formed at

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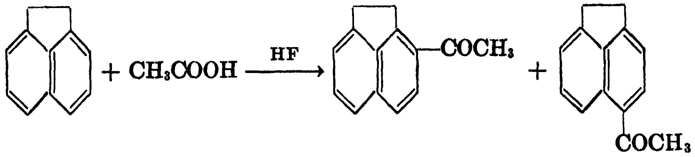
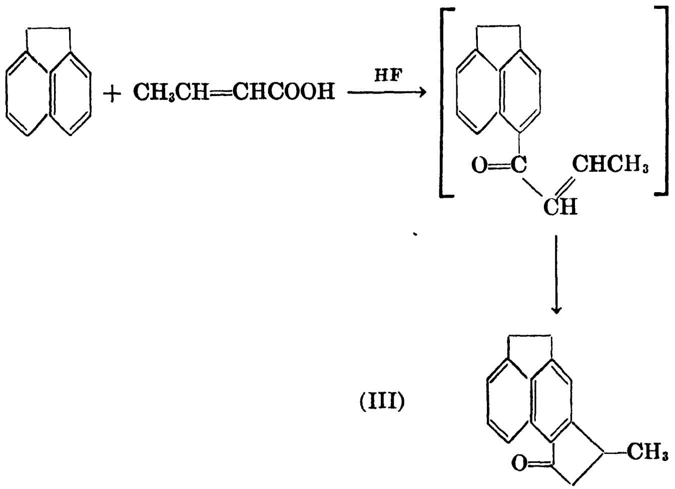
[122] Simons and Passino, *J. Am. Chem. Soc.*, 62, 1624 (1940).
[123] Simons, Randall, and Archer, *J. Am. Chem. Soc.*, 61, 1795 (1939).
[124] L. F. Fieser and Kilmer, *J. Am. Chem. Soc.*, 62, 1354 (1940).



(I) (II)

the same time in a yield of 43%.[125] The 3-derivatives are always formed in Friedel-Crafts reactions with aluminum chloride, and acenaphthene derivatives substituted in the 1-position have not been available by its use. In general, other reactions involving acenaphthene had not given 1-derivatives up to the time this reaction was discovered. Fieser attributed the good yield of 1-acetoacenaphthene to two factors: that it was formed more easily and that it was insoluble in the reaction mixture.[124]

Crotonic acid acylated acenaphthene in the 3-position, but the product cyclized immediately, and the product isolated was 1′-methyl-3′-keto-2,3-cyclopentanoacenaphthene (III).[120] Condensations with formic and malonic acids and with maleic and phthalic anhydrides also probably could be effected.



(III)

Acenaphthene, perinaphthane, and hydrindene were unique among all the hydrocarbons studied, since good yields of the acyl derivatives were obtained at room temperature.[125] The yields were not dependent on the acylating agent used.

The reactions between naphthalene and acetic anhydride and between phenanthrene and acetic acid required heating of the solutions in hydrogen fluoride to 50° to 60°C. under pressure, and afforded poorer yields of the acyl derivatives. The following compounds did not react under any conditions when treated with hydrogen fluoride: benzene and phthalic anhydride or benzoic acid, naphthalene and crotonic acid or succinic anhydride, phenanthrene and acetyl chloride or β-chloropropionyl chloride, anthracene and chloroacetyl chloride, 1,2-benzanthracene and oxalic acid.

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[125] L. F. Fieser and Hershberg, *J. Am. Chem. Soc.*, 62, 49 (1940).

4. Alkylation of Aromatic Compounds

The alkylation of aromatic compounds in the presence of hydrogen fluoride has been effected by a wide variety of reagents. Among these are alkyl and aralkyl halides,[120,126] olefins and their derivatives (allyl alcohol, allyl halides, cinnamic and oleic acids),[120,126–128] alcohols,[120,128,129] ethers,[120,128,129] esters,[120,130] cyclopropane,[131] and ethylene oxide.[120,128] These reactions and the ranges of yields obtained by the various alkylating agents are summarized in the following equations:

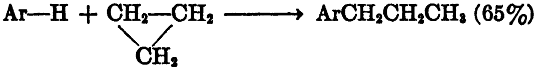
$$\text{Ar—H} + \text{R'Cl} \longrightarrow \text{Ar—R'} + \text{HCl (10 to 75\%)} \qquad (1)$$

$$\text{Ar—H} + \text{R'CH}{=}\text{CH}_2 \longrightarrow \text{ArCH}_2\text{CH}_2\text{R' (25 to 98\%)} \qquad (2)$$

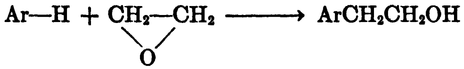
$$\text{Ar—H} + \text{R'OH} \longrightarrow \text{Ar—R'} + \text{H}_2\text{O (3 to 97\%)} \qquad (3)$$

$$\text{Ar—H} + \text{R'OR'} \longrightarrow \text{Ar—R'} + \text{R'OH (20 to 76\%)} \qquad (4)$$

$$\text{Ar—H} + \text{R''COOR'} \longrightarrow \text{Ar—R'} + \text{R''COOH (53 to 75\%)} \qquad (5)$$



(6)



(7)

The alcohol formed in Reaction 4 can alkylate more of the aromatic substance. Acylation is a competing reaction when esters are used (Eq. 5).

Simons found that the alkyl chlorides were more useful for alkylations than the bromides and iodides.[122] The ease of reaction also increased with the extent of branching of the chain. Thus tertiary chlorides reacted at 0°C., and secondary chlorides effected alkylations slowly at 25°, but primary chlorides required the use of higher temperatures and pressures.[126] The alcohols and ethers exhibited a similar behavior; the tertiary and secondary alcohols and their ethers reacted at room temperature, but the primary alcohols and ethers with the exception of benzyl alcohol and its ethers showed no tendency to alkylate aromatic compounds under 100°.[129] In general the alcohols gave better yields at room temperature than did the halides[129]; the reverse is true when aluminum chloride is the condensing agent. Calcott found no great differences in the various reagents and reported that olefins, alcohols, ethers, and esters are equally useful for alkylations. The use of olefins is to be preferred when polyalkylated products are desired.[120,128]

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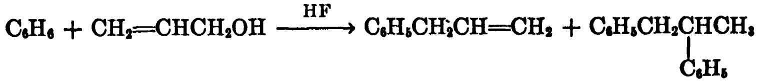
[126] Simons and Archer, *J. Am. Chem. Soc.*, 60, 986, 2952 (1938).
[127] Simons and Archer, *J. Am. Chem. Soc.*, 61, 1521 (1939).
[128] E. I. du Pont de Nemours and Co., U. S. Patent, 2,275,312.
[129] Simons and Archer, *J. Am. Chem. Soc.*, 62, 1623 (1940).
[130] Simons, Archer, and Randall, *J. Am. Chem. Soc.*, 61, 1821 (1939).
[131] Simons, Archer, and Adams, *J. Am. Chem. Soc.*, 60, 2955 (1938).

The reactions involving the introduction of ethyl, amyl, octyl, cyclohexyl,[122,132] and hexyl[133] groups were studied exhaustively, and good yields were obtained with the various alkylating agents. No arylations could be effected with phenol, phenyl acetate, chlorobenzene, or diphenyl ether even at temperatures as high as 200°C. Attempts to methylate aromatic compounds by methanol, methyl iodide, and methyl acetate were also unsuccessful[122]; in contrast to this, such alkylations catalyzed by aluminum chloride proceed very well. Calcott showed that the alkylating agents had to contain at least 2 carbon atoms, and the compounds which gave the best results were derivatives of propane.[120] The quantities of the alkylating agents were varied in accordance with the extent of alkylation desired; usually molar quantities or less of them were added to the reaction mixtures.

This method has been used for the alkylation of aromatic hydrocarbons, phenols and their nitro and amino derivatives, phenol ethers, aromatic acids, hydroxy acids, sulfonic acids,[120] and such unsaturated compounds as cyclohexene and trimethylethylene.[134] Reactions involving both groups frequently take place with bifunctional alkylating agents.



$$C_6H_6 + CH_2{=}CHCH_2OH \xrightarrow{HF} C_6H_5CH_2CH{=}CH_2 + C_6H_5CH_2\underset{\substack{|\\ C_6H_5}}{C}HCH_3$$

Allyl alcohol reacts with benzene with the production of allylbenzene (11 to 20%) and 1,2-diphenylpropane (8 to 12%). A compound such as cinnamic acid reacts with benzene with the production of only one of the

$$C_6H_6 + C_6H_5CH{=}CHCOOH \xrightarrow{HF} (C_6H_5)_2CHCH_2COOH$$

two isomers which might be expected from the alkylation, and 3,3-diphenylpropionic acid is formed in a yield of 53%. The carboxyl group prevents substitution on the α-carbon atom.[127] Occasionally ring closures result from reactions involving bifunctional alkylating agents, as is shown by the formation of perinaphthane from naphthalene and allyl chloride.[135]

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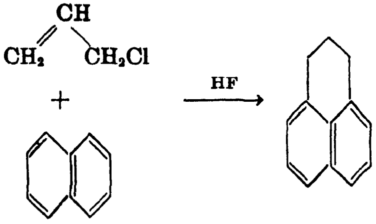
[132] Simons and Bassler, *J. Am. Chem. Soc.*, 63, 880 (1941).

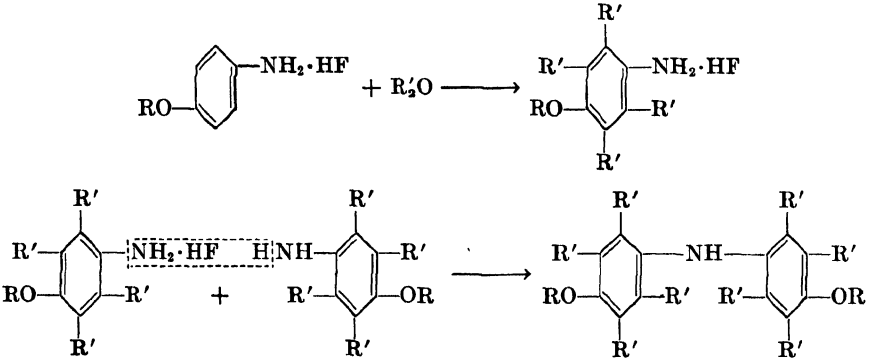
[133] Spiegler and Tinker, *J. Am. Chem. Soc.*, 61, 1002 (1939).

[134] Simons, Archer, and Passino, *J. Am. Chem. Soc.*, 60, 2956 (1938).

[135] L. F. Fieser, Joshel, and Seligman, *J. Am. Chem. Soc.*, 61, 2134 (1939).



The production of *N*-alkyl intermediates in the alkylation of amines does not take place, but occasionally a diphenylamine derivative results from the condensation of 2 moles of the amine by the elimination of ammonium fluoride. This is the way in which 4,4′-dihydroxytetraisopropyldiphenylamine (61%) or its dimethyl ether (50%) are formed along with the normal products expected from the alkylation of *p*-aminophenol or *p*-anisidine by isopropyl ether.[120] Usually alkylations involving hydrogen fluoride as the catalyst afford the same products as those obtained by the use of aluminum chloride, boron fluoride, or sulfuric acid.



R = H—, CH₃— R′ = *i*-C_3H_7—

A kinetic study of the alkylation of toluene by *tert*-butyl chloride was made by Sprauer and Simons[136] by observing the rise in pressure caused by the hydrogen chloride liberated in the reaction. Recently this work was repeated with a more refined apparatus and the essential correctness of the equations and theory developed from the earlier work was confirmed.[137] The reaction, which goes to completion in the homogeneous medium employed, was shown to be a first order one. The addition of small quantities of water, methanol, ether, or hexamethylacetone accelerated the reaction to a great extent. Mechanisms which postulate ions or free radicals as intermediates were shown to be untenable from energy considerations.

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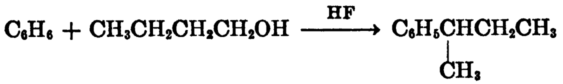
[136] Sprauer and Simons, *J. Am. Chem. Soc.*, 64, 648 (1942).
[137] Pearlson and Simons, *J. Am. Chem. Soc.*, 67, 352 (1945).

The action of hydrogen fluoride probably depends on its tendency to effect proton transfers.

Alkylations involving the use of alkyl halides or olefins are catalyzed by very small quantities of hydrogen fluoride.[126] Larger amounts of hydrogen fluoride are necessary for reactions in which oxygen containing alkylating agents are employed, partly because the acid forms an oxonium salt by addition to the oxygen atom. Furthermore, more hydrogen fluoride is needed to combine with the water liberated in these reactions.[134]

The products formed in alkylation reactions depend not only on the duration of the time of contact with the catalyst (1 to 20 hours) but also on the quantity and state of dilution of the hydrogen fluoride used. Phenol reacts with diisobutylene in the presence of large quantities of hydrogen fluoride to produce only *p-tert*-butylphenol, but the use of a small amount of 70% hydrofluoric acid leads to the formation of a 33.3% yield of *p-tert*-octylphenol. The reactions with triisobutylene are very similar.[138] Calcott obtained only the *tert*-butyl derivative in his work.[120]

It is interesting that a few compounds which normally undergo condensation and polymerization in the presence of hydrogen fluoride have been used successfully in alkylation reactions. Butyl and amyl chlorides produced chlorides with both longer and shorter chains when treated with hydrogen fluoride alone, but they behaved normally when benzene was alkylated by them; no pentyl- or hexylbenzenes or the like were formed.[126] Benzyl alcohol is resinified very rapidly by hydrogen fluoride, but it reacted with benzene normally in a yield of 65 to 70% and no polymer was obtained.[129] Although Calcott reported that neither isomerization nor migration of alkyl groups took place in reactions catalyzed by hydrogen fluoride,[120] a few examples of isomerization at higher temperatures were observed by Simons. The alkylation of benzene by *n*-butyl alcohol or by *n*-butyl acetate at 100°C. gave *sec*-butylbenzene,[130] and the reaction with *n*-propyl alcohol afforded isopropylbenzene.



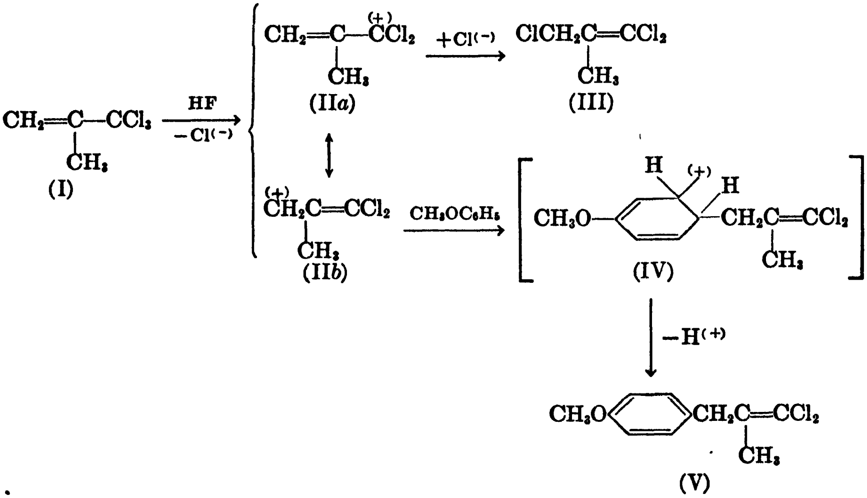
$$C_6H_6 + CH_3CH_2CH_2CH_2OH \xrightarrow{HF} C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_3$$

The ethers reacted similarly.[129] At one time it was thought that these reactions proceeded by an olefin intermediate, but the production of *sec*-butylbenzene with a small but definite optical rotation by the alkylation of benzene with optically active *sec*-butyl alcohol lends support to the positive cation mechanism.[139] That some racemization must be expected before alkylation can take place was shown by experiments with the optically ac-

[138] Simons and Archer, *J. Am. Chem. Soc.*, 62, 451 (1940).
[139] Burwell, Jr., and Archer, *J. Am. Chem. Soc.*, 64, 1032 (1942).

tive alcohol and hydrogen fluoride alone.[140] This is also explainable by the ionic mechanism.

The alkylation of anisole by 2-trichloromethylpropene (I) has been studied by Price and Marshall. The hydrogen-fluoride-catalyzed reaction went smoothly with the production of V in a yield of 38%. They postulated the accompanying mechanism for the alkylation. The removal of a chloride ion from I gives a resonating structure (II*a* ⟷ II*b*) which is common to both the allylic rearrangement and the alkylation reaction. In the absence of anisole, III is formed. Under the same conditions III alkylated anisole to the extent of only 5%.[141]



At first it was assumed that the alkylations were affected by alkyl fluorides formed by reactions between the alkylating agents and hydrogen fluoride.[17,120] This mechanism seemed plausible for alkylations by olefins, cyclopropane, and ethylene oxides, but such an assumption appeared to be untenable for the alcohols and ethers, since they form alkyl fluorides by reactions with hydrogen fluoride only with considerable difficulty. On the other hand, it seems significant that olefins are better alkylating agents than are alkyl halides.[132] Another theory assumes the formation of olefin intermediates in the reaction and the alkylation of the aromatic hydrocarbons by them; but the dehydration of alcohols under the conditions under which these reactions are effected has never been observed. Furthermore, the olefin mechanism is impossible in the case of an alkylating agent such as benzyl alcohol.

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[140] Burwell, Jr., *J. Am. Chem. Soc.*, 64, 1025 (1942).
[141] Price and Marshall, *J. Org. Chem.*, 8, 532 (1943).

The mechanism probably involves the formation of an intermediate organic complex ion. These complex ions add to a double bond of the benzene nucleus with subsequent elimination of the proton and water. A similar mechanism has been postulated for the Friedel-Crafts reaction.[142] This mechanism does not conflict with the experimental results mentioned above[130,131,134] and it also agrees with the theory developed by Fredenhagen for the dissociation of organic compounds in hydrogen fluoride.[88]

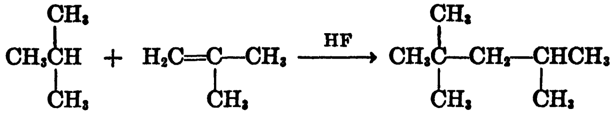
$$ROH + HF \longrightarrow ROH_2^+ + F^-$$

$$RCOOR' + 2HF \longrightarrow RCOOH_2^+ + R'^+ + 2F^-$$

5. Alkylation of Paraffin Hydrocarbons

Although a considerable amount of research had been done prior to 1941 on the hydrogen-fluoride-catalyzed reaction between olefins and isoparaffins for the production of highly branched paraffin hydrocarbons, the application of the method for the production of high octane aviation gasolines was delayed because of the lack of experience in the industry in handling liquid hydrogen fluoride.[143] Other catalysts which had been found to effect the alkylation reaction were aluminum chloride, sulfuric acid, zirconium chloride, and boron fluoride, of which only the first two were used commercially.[2,144] The greatly increased demand for aviation gasoline during the war stimulated the construction of plants using the hydrogen fluoride process, and they played an important part in the manufacture of high octane fuels. For security reasons practically nothing was published about the process until recently.

The alkylation reaction may be regarded as an addition of the isoparaffin to the olefin double bond. Reactions have been carried out with isobutane and olefins, such as propylene, the butylenes, and 2-pentene, and with isopentane and propylene.[144] The alkylation usually is not simple and a number of other reactions can take place simultaneously; however, the side reactions can be minimized, by proper choice of conditions, to such an extent that the yield of the primary alkylation product (the addition of 1 mole of isobutane to the olefin) is 80% or better. The factors favoring primary alkylation are the use of moderate temperatures (20° to 45°C.)



$$CH_3CH(CH_3)CH_3 + H_2C{=}C(CH_3)CH_3 \xrightarrow{HF} CH_3C(CH_3)_2{-}CH_2{-}CH(CH_3)CH_3$$

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[142] Hückel, *Theoretische Grundlagen der organische Chemie*, 4th ed., Akadem. Verlagsgesellschaft, Leipzig, 1943, Vol. I, p. 591.

[143] Gerhold, Iverson, Nebeck, and Newman, *Trans. Am. Inst. Chem. Eng.*, **39**, 793 (1943).

[144] Universal Oil Products Co., U. S. Patent, 2,267,730.

and a high ratio of isoparaffin to olefin (1.5 and greater). Usually the product is completely saturated, contains only traces of fluorinated compounds (less than 0.01%), and it boils in the gasoline range. In the alkylation of isobutylene with isobutane the product consists primarily of the 2,2,4-trimethyl- and 2,3,4-trimethylpentanes.[2]

Other reactions which may take place are overalkylation (the reaction of the primary product with another molecule of the olefin), cracking of the products, addition of hydrogen fluoride to the olefin with the formation of an alkyl fluoride, polymerization of the olefin, isomerization, and various hydrogen transfer reactions. The formation of alkyl fluorides is not detrimental to the reaction, since it has been shown that alkyl fluorides alkylate isobutane and isopentane under the conditions of the alkylation reaction as long as sufficient hydrogen fluoride is present.[145]

In the production of high octane fuels isobutane is used almost exclusively because of its reactivity, its availability, and the high octane rating of the product. A number of olefins give good products (propylene, amylenes, butylenes), but butylene is employed most extensively, since it is also readily available from refinery butane-butylene fractions, which contain both reactants.[146]

In the industrial process[146] the liquid hydrocarbon is agitated with liquid hydrogen fluoride under pressure until a temporary emulsion is obtained, so that the isobutane may have ready access to the acid phase. The emulsion is circulated vigorously to insure distribution of the olefin in a low concentration as it is added and to discourage its polymerization. An excess of isobutane is maintained to minimize further alkylation of more olefin by the primary product. Refrigeration is unnecessary, as water cooling is sufficient to keep the temperature within the desired limits (20° to 45°C.). The acid does not necessarily have to be anhydrous; it is usually maintained at a strength of 85 to 90%.

The hydrogen fluoride process is vastly superior to the older methods of alkylation for a number of reasons. As was just mentioned, the refrigeration which is so necessary to the sulfuric acid process is unnecessary. Unlike the sludges resulting from the other processes, the high boiling polymeric materials (which contain alkyl fluorides and are soluble in liquid hydrogen fluoride) resulting from side reactions in the hydrogen fluoride alkylations are decomposed easily by heating. The recovery of the hydrogen fluoride regenerated makes the catalyst consumption very low. Furthermore, this recovery process minimizes the problems of disposal encountered with the acid sludges.

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[145] Universal Oil Products Co., U. S. Patent, 2,307,799.

[146] Frey, *Chem. & Met. Eng.*, 50, No. 11, 126 (1943). For a recent more complete summary of the industrial process see *Hydrofluoric Acid Alkylation*, Phillips Petroleum Co., Bartlesville, Oklahoma (1946).

The chemical stability and physical properties of hydrogen fluoride make it usable over a wide range of conditions; thus the most economical conditions or those most satisfactory thermodynamically can be employed without regard to possible effects on the catalyst. Its vapor pressure is low enough so that only moderate pressures are required to keep it in the liquid state, and its freezing point is low enough to permit much lower temperatures of operation than those for other catalysts which become viscous. Although for most alkylations in which hydrogen fluoride is used temperatures of about 25°C. are most desirable, a few reactions are favored by much lower temperatures.

One of the most important advantages which the hydrogen fluoride process has over the others is the fact that its corrosive action on the steels used in refinery equipment is so low. Actual plant experience has shown hydrogen fluoride to be far superior to sulfuric acid in this respect. The hazards in handling hydrogen fluoride have not been serious, and the safety records of plants employing the hydrogen fluoride process have been excellent.

In order to gain a better understanding of the alkylation reaction Pines and Ipatieff have studied the reaction between cycloparaffins and olefins.[147] A large amount of the work was carried out with sulfuric acid, but one reaction between methylcyclopentane and a mixture of *n*-butenes in hydrogen fluoride was carried out. At 55° to 65°C. a complex reaction took place which produced a mixture of paraffins corresponding to octanes, alkylated cyclohexanes of the formula $C_{10}H_{20}$, and dicyclic hydrocarbons corresponding to methylcyclopentylcyclohexane. A mixture of unsaturated hydrocarbons containing an average of two double bonds per molecule was also obtained from the products of the reaction. A mechanism involving carbonium ion intermediates was advanced to explain the ring enlargement. In a patent based upon this work the use of a boron fluoride-hydrogen fluoride catalyst was recommended.[148]

The addition of alkyl halides to olefins in hydrogen fluoride solution has been effected in one case but the yields were very poor. The reaction between *tert*-butyl chloride and cyclohexene gave cyclohexyl chloride (65%), cyclohexyl fluoride (11.5%), and 1-chloro-3-*tert*-butylcyclohexane (11%). The cyclohexyl chloride probably resulted from the removal of hydrogen chloride from the alkyl halide and its addition to cyclohexene. An inseparable mixture of chloroolefins was also obtained, which was similar to the product obtained from the action of hydrogen fluoride on *tert*-butyl chloride alone.[149]

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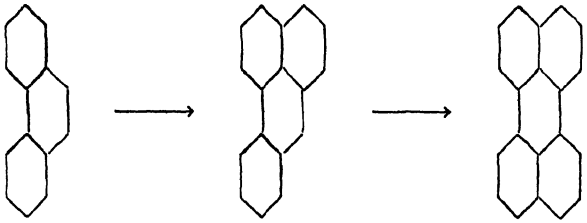
[147] Pines and Ipatieff, *J. Am. Chem. Soc.*, **67**, 1631 (1945).
[148] Universal Oil Products Co., U. S. Patent, 2,340,557.
[149] Simons and Meunier, *J. Am. Chem. Soc.*, **65**, 1269 (1943).

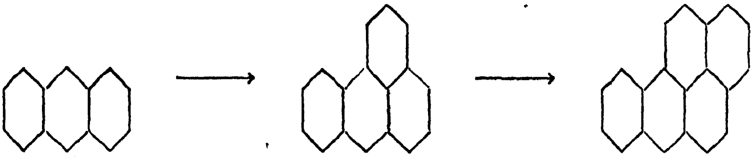
6. Ring Closure

The ring-closure reactions catalyzed by hydrogen fluoride fall into two general types. In one, peri condensations with polynuclear aromatic compounds are effected by the use of bifunctional molecules, while in the other the reaction is essentially one of intramolecular acylation. On the borderline between these two are condensations involving crotonic acid with polynuclear substances which may be considered either as alkylation reactions followed by intramolecular acylation or as acylation reactions followed by intramolecular alkylation.

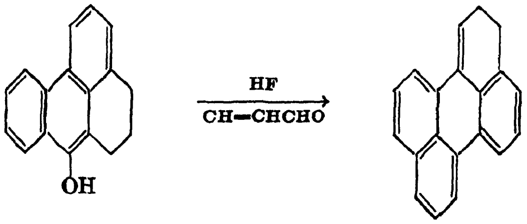
The first type of reaction is illustrated by the peri condensations of polynuclear aromatic compounds with acrolein. According to the conditions of the reaction and the particular aromatic substances involved, the condensation of 1 or 2 moles of acrolein can be effected. Thus, phenanthrene (I) gave a partially hydrogenated perylene (II) and 9,10-dihydroanthracene (III) was converted to a partially reduced 3,4-benzopyrene (IV), as shown in the accompanying schematic formulae.[20] The positions of the double bonds are not shown, since the products were not identified but were dehydrogenated to the corresponding aromatic substances. Allyl com-



(I) (II)



(III) (IV)

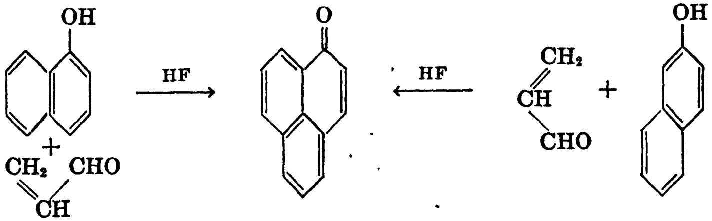


(V) (VI)

pounds and derivatives of acrolein are also usable in condensations of this type.[135] A hydroxyl group in one of the peri positions does not prevent the reaction, since 1,10-trimethylene-9-hydroxyphenanthrene (V), a reduction product of benzanthrone, gave a dihydroperylene (VI).[20,150] In contrast to these reactions with hydrogen fluoride, it has not been possible to effect the addition of more than 1 mole of acrolein to any of these aromatic compounds by the action of sulfuric acid.

Usually the condensations were effected by the use of an excess of acrolein and a 3- to 16-fold quantity of hydrogen fluoride at room temperature. The time necessary for completion of the reactions varied from 1 to 24 hours. Anhydrous hydrogen fluoride was not always essential, since in some cases 80% aqueous acid was effective in causing condensations.

In addition to these reactions already mentioned, condensations have been carried out with acenaphthene and with the α- and β-naphthols. Acenaphthene afforded a mixture of substances showing a characteristic brilliant green color with sulfuric acid, but from which no identifiable products were isolated. Both the isomeric naphthols gave the same product, perinaphthenone (VII), rather than the saturated ketone in reactions with acrolein in hydrogen fluoride.[20]



(VII)

In the reactions with acrolein Calcott believed that the mechanism involved alkylation with a subsequent condensation involving the aldehyde group.[20] The possibility of the formation of aldol-like intermediates, as formulated by Bally and Scholl, must also be considered in these reactions.[151] Whether or not this is the mechanism and whether aldol intermediates are involved has not been determined.

Another peri condensation which is not an alkylation but a dehydrogenation has been reported in the patent literature. When 1,1′-binaphthyl (VIII) was heated with hydrogen fluoride in an autoclave, perylene (IX) was formed.[152]

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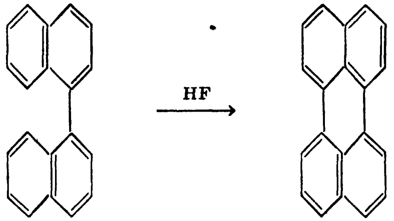
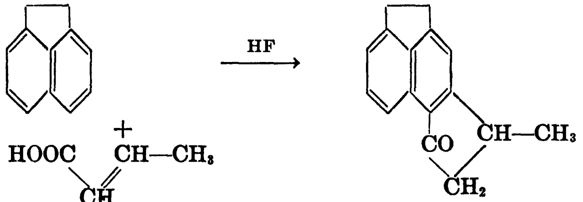
[150] E. I. du Pont de Nemours and Co., U. S. Patent, 2,145,905.
[151] Bally and Scholl, *Ber.*, 44, 1656 (1911).
[152] E. I. du Pont de Nemours and Co., U. S. Patent, 2,250,394.



(VIII) (IX)

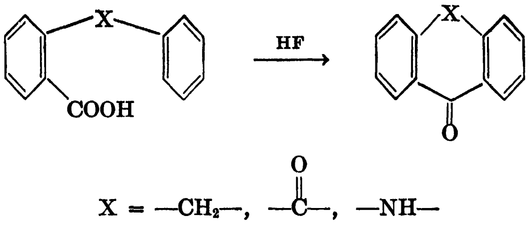
The reaction between crotonic acid and acenaphthene did not result in any peri condensation, as might be expected from the foregoing discussion, but a 62% yield of 1′-methyl-3′-keto-2,3-cyclopentanoacenaphthene (X) was obtained.[97]



(X)

A similar condensation with phenanthrene gave a corresponding mixture of methylketocyclopentanophenanthrenes in a yield of 26%. Fieser believed that the reaction was one of acylation followed by an intramolecular alkylation,[97] but Calcott's observations that alkylations are more easily effected than acylations in hydrogen fluoride would lead to the opposite conclusion.[20] The sequence of these steps is still not definitely established.

The second type of ring closure involves intramolecular acylations, which are divided conveniently into two groups: those with arylcarboxylic acids and those with β- or γ-aryl-substituted aliphatic acids. The first group consists of compounds of the type of benzophenone-, diphenylmethane-, and diphenylamine-2-carboxylic acids which form derivatives of anthraquinone, anthrone, and acridone on ring closure.[16,97,153] Various



$$X = -CH_2-,\ -\overset{O}{\overset{\|}{C}}-,\ -NH-$$

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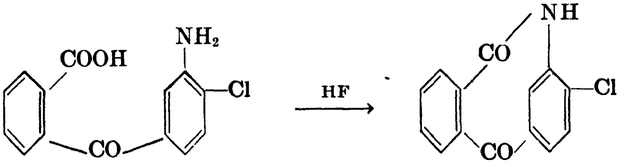
[153] L. F. Fieser and Heyman, *J. Am. Chem. Soc.*, **63**, 2333 (1941).

derivatives of the acids such as the salts, chlorides, esters, and amides can be used in place of the free acids.

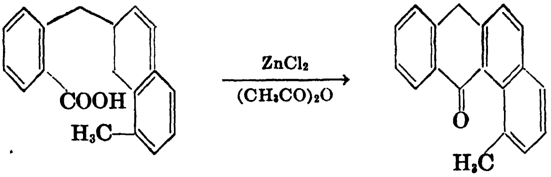
The condensations may be carried out at room temperature by dissolving the acid in 10 to 20 times its weight of liquid hydrogen fluoride and allowing the solution to stand for 1 hour. The product is isolated by evaporating the hydrogen fluoride or by pouring the solution on ice. The yields vary from 58 to 75%. The reactions may be effected at 100° to 130°C. under pressure, a method which usually gives yields of over 80% even with quantities of hydrogen fluoride only 3 to 4 times the weight of the organic substance.

Since liquid hydrogen fluoride readily dissolves most of the compounds used in these reactions, the condensations take place in homogeneous media, and the yields are excellent. It is usually advisable to keep the water content of the medium as low as possible, but successful condensations have been effected with 42% aqueous hydrofluoric acid in certain cases. A marked decrease in the rate of the reaction is caused by an increased water content, and heating under pressure is often necessary to complete condensations in which considerable quantities of water are present.

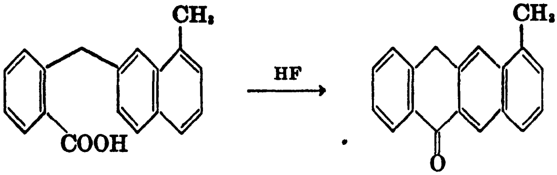
The acylation does not always take place in the direction expected and sometimes cannot be effected at all. *o*-Benzoylbenzoic acid could not be converted to anthraquinone by hydrogen fluoride,[97] although certain of its derivatives underwent ring closure. When there was an amino group in the 3′ position, the acylation of the aromatic nucleus did not take place, but a cyclic amide was obtained.[16]



When zinc chloride in acetic anhydride was used for the cyclization of 2-(8-methyl-2-naphthylmethyl)benzoic acid (XI), the product was a methyl-1,2-benzanthranyl acetate (XII*a*), but the action of hydrogen fluoride closed the ring in the β position with the formation of 1′-methyl-2,3-benzanthrone (XII*b*) as the main product.[125]

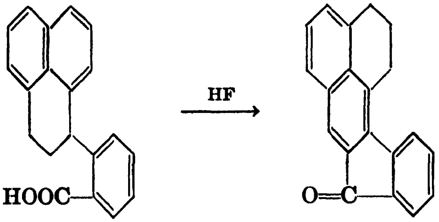


(XI) (XII*a*)



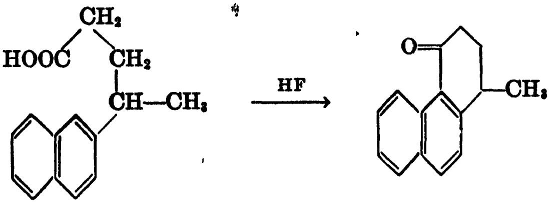
(XI) (XIIb)

A migration of double bonds probably takes place during the cyclization of 1-(2-carboxyphenyl)perinaphthane (XIII), since the reaction with hydrogen fluoride gave 4,4′-trimethylene-2,3-benzofluorenone (XIV) instead of the 1′,9-dimethylene-1,2-benzanthrone expected.



(XIII) (XIV)

Intramolecular acylations of aryl-substituted fatty acids have been studied quite extensively by Fieser and have been extended to derivatives of benzene, acenaphthene, biphenyl, phenanthrene, pyrene, retene, naphthalene, and the benzanthracenes. Products obtained in this way include tetralone, hydrindone, hydrogenated ketones of 1,2-benzanthracene, pyrene, benzopyrene, and triphenylene.[97,153,154] The reaction is carried out by the method outlined previously for quantities of hydrogen fluoride of from 7 to 30 times the weight of the acid and with allowance of 1 to 26 hours for the completion of the condensation. The yields usually are above 70%. An example of the reaction is the intramolecular acylation of γ-(2-



(XV) (XVI)

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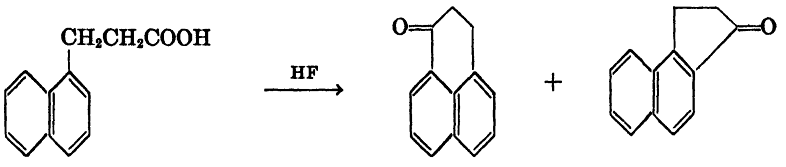
[154] L. F. Fieser and W. S. Johnson, *J. Am. Chem. Soc.*, 61, 1647 (1939); L. F. Fieser and Joshel, *ibid.*, 61, 2958 (1939); L. F. Fieser and Clapp, *ibid.*, 63, 319 (1941); L. F. Fieser and Daudt, *ibid.*, 63, 782 (1941); L. F. Fieser and Jones, *ibid.*, 64, 1666 (1942). For a review of ring closures with use of hydrogen fluoride see W. S. Johnson, in *Organic Reactions*, Wiley, New York, 1944, Vol. II, p. 157.

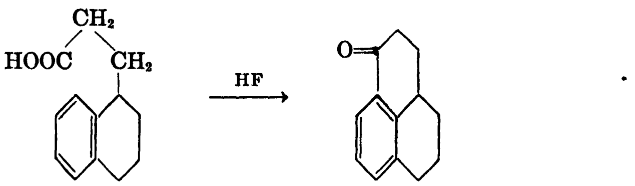
naphthyl)valeric acid (XV) which is cyclized to 4-keto-1-methyl-1,2,3,4-tetrahydrophenanthrene (XVI) in a 93% yield.[155]

Intramolecular acylations involving the peri positions do not give clean products, since ring closure may take place not only in the peri position but also in the position ortho to the place of attachment of the fatty acid. Thus β-1-naphthylpropionic acid gave a mixture of isomeric ketones in a yield of 81 to 93%.[156] From the mixture could be isolated 81% of perinaphthanone (XVII) and a 6% yield of 4,5-benzohydrindone-1 (XVIII) (formed by ring closure in the 2 position). Attempts to cyclize the acid chloride (prepared by the use of phosphorus pentachloride) by aluminum or stannic chloride gave very poor yields.

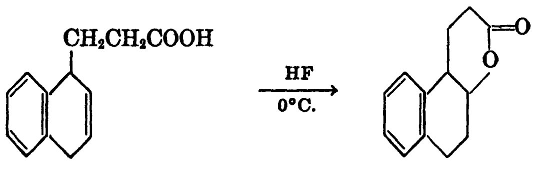


(XVII) (XVIII)

The intramolecular acylation of the tetrahydro derivative of the acid (XIX) resulted in ring closure with the production of the expected ketone in a yield of 99%. Treatment of the dihydro compound (XXI) with hydrogen fluoride at 0°C. for a few minutes gave a 94% yield of the lactone (XXII), but when the solution of the acid was allowed to stand at room temperature for 16 hours a mixture of ketones was obtained. Separation of the components of the product gave the saturated ketone (XX), a dihy-



(XIX) (XX)



(XXI) (XXII)

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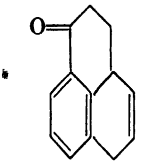
[155] W. S. Johnson, Goldman, and Schneider, *J. Am. Chem. Soc.*, 67, 1357 (1945).

[156] L. F. Fieser and Gates, *J. Am. Chem. Soc.*, 62, 2335 (1940); L. F. Fieser and Novello, *ibid.*, 62, 1855 (1940); Lock and Walter, *Ber.*, 75, 1163 (1942).

droperinaphthanone (possibly XXIII), and 3′-keto-3,4-dihydro-1,2-cyclopentanonaphthalene (XXIV).[157]



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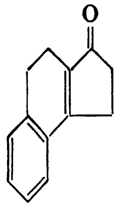
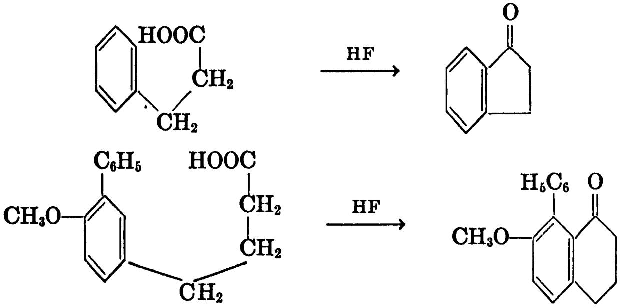


(XXIV)

Hydrogen fluoride has been shown to be a very desirable reagent for effecting these ring-closure reactions. In some cases in which the older methods were unsuccessful, cyclizations have been effected by hydrogen



fluoride. Examples of this are the condensations of hydrocinnamic acid to hydrindone and of γ-(4-methoxy-3-phenyl)butyric acid to 5-methoxy-8-phenyltetralone.[97] Its chief advantage over the Friedel-Crafts reaction and over methods in which phosphorus pentoxide or sulfuric acid are employed is the convenience with which the condensation can be effected and the ease with which the products are isolated. Often, when very pure starting materials are used, the products are nearly analytically pure, and rarely are tarry residues obtained.

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[157] W. S. Johnson, H. C. E. Johnson, and Petersen, *J. Am. Chem. Soc.*, 67, 1360 (1945).

Methods for the Thiocyanation of Organic Compounds

By H. P. KAUFMANN

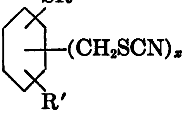
Translated and revised by ROGER J. TULL

The importance of suitable methods for the thiocyanation of organic compounds is evident from a recent review.[1] Considerable progress has been made on this reaction during the last two decades. The methods to be used must be judged for each individual case. Older methods are still useful after suitable adaptation. Inasmuch as they are fairly well known, the old methods will only be briefly reviewed in this chapter; interesting examples from the recent literature will be used.

I. OLD METHODS OF THIOCYANATION

The classical method for the thiocyanation of aliphatic compounds involves the reaction of aliphatic halides with inorganic thiocyanates, whereby the halogen is replaced by the thiocyanate group. This reaction can also be applied to polyhalogen compounds.[2] Methylene chloride, ethylene chloride, benzal chloride, *m*-cyanobenzal chloride, and dichloropicoline react readily to form the corresponding dithiocyanates. The preparation of 2,3-dithiocyanobutane has been described by Likhosherstov and Butrimov.[3] Furthermore, the preparation of polythiocyanates from halides whose halogens are attached to non-adjacent carbon atoms, and whose molecule also contains —OR, —S—, —SO—, —COO—, —CO—, —OH—, or —NH_2 groups, has been protected by patent.[4]

Insecticides having the general formula I have been prepared under



(I)

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[1] *Angew. Chem.*, **54**, 168 (1941).

[2] German Patent, 545,740 (Schering-Kahlbaum A.-G.).

[3] Likhosherstov and Butrimov, *Acta Univ. Voronegiensis*, **8**, No. 4, 86 (1935); *Chem. Zentr.*, **1937**, I, 1924; *Chem. Abstracts*, **32**, 6624 (1938).

[4] U. S. Patents, 2,077,478, 2,077,479.

suitable conditions by treatment of the corresponding chloromethyl thioether with an inorganic thiocyanate.[5] In analogy, Wagner-Jauregg, Arnold, and Hippchen[6] recently prepared oleyl thiocyanate, chaulmoogryl thiocyanate, and similar esters as well as cholesteryl thiocyanate from the corresponding halogen derivatives. These compounds were tested on leprosy in rats.

The thiocyanate group can be introduced into hydroxyl compounds, *e.g.*, mono- and diglycerides are esterified with chloroacetic acid and the chlorine of the chloroacetic ester is replaced by the thiocyanate group.[7] The replacement reaction has also been employed in the preparation of polyhalogenphenoxythiocyanoalkyl ethers, *e.g.*, β-(2,4,6-trichlorophenoxy)-β′-thiocyanodiethyl ether, and ethers such as β-(2-cyclohexylphenoxy)-β′-thiocyanodiethyl ether.[8]

The inorganic acid group in alkyl sulfates is replaced smoothly by the thiocyanate group. According to a recent patent, this reaction requires care, and the temperature must be held slightly above 0°C. Thus, *tert*-amyl thiocyanate can be obtained from *tert*-amyl sulfate.[9]

The Sandmeyer reaction has also retained its importance in the preparation of thiocyanates. In this way, 5-thiocyanosalicylic acid,[10] 4-thiocyanoanisole, or phenetole,[11] can be prepared with the corresponding isothiocyanates as by-products.

Braun and Engelbertz[12] obtained thiocyanates from organic sulfides and cyanogen bromide. Also, cyanogen halides and mercaptides of heavy metals can be used.[13]

Footner and Smiles have found that organic thiosulfates will react with alkali cyanides to form thiocyanates.[14]

$$RS{-}SO_3Na + NaCN \longrightarrow RSCN + Na_2SO_3$$

This reaction proceeds smoothly with the formation of pure products. It is a good method when the corresponding thiosulfates are available.

It has been pointed out that the use of chlorothiocyanogen in the thiocyanation reaction may be of some value.[15] Recently, the discovery of free thiocyanogen and the study of its properties have proved to be a fundamental advancement which has attracted a great deal of attention.

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[5] U. S. Patent, 1,841,458 (Winthrop Chemical Co.).

[6] Wagner-Jauregg, Arnold, and Hippchen, *J. prakt. Chem.*, **155**, 216 (1940).

[7] Epstein and Harris, U. S. Patent, 2,123,186.

[8] U. S. Patents, 2,201,156, 2,201,157 (Dow Chemical Co.).

[9] Walden, *Ber.*, **40**, 3214 (1907).

[10] Kaufmann and Rossbach, *Ber.*, **58**, 1556 (1925).

[11] Dienske, *Rec. trav. chim.*, **50**, 407 (1931).

[12] Von Braun and Engelbertz, *Ber.*, **56**, 1573 (1923).

[13] British Patent, 431,064 (Graselli Chemical Co.).

[14] Footner and Smiles, *J. Chem. Soc.*, **127**, 2887 (1925).

[15] Kaufmann and Liepe, *Ber.*, **57**, 923 (1924); **60**, 58 (1927); Lecher and Joseph *Ber.*, **59**, 2603 (1926).

II. THIOCYANATION WITH FREE THIOCYANOGEN

Almost simultaneously, Bjerrum and Kischner[16] and Söderbäck[17] found that under certain conditions thiocyanogen, $(SCN)_2$, is capable of existence. Söderbäck succeeded in isolating the compound in crystalline form with a melting point of −2° to −3°C. by treating lead thiocyanate with bromine in an inert solvent:

$$Pb(SCN)_2 + Br_2 \longrightarrow PbBr_2 + (SCN)_2$$

Unfortunately, thiocyanogen is a highly unstable compound. In the presence of water, hydrolysis occurs immediately, as shown in the following equation[18]:

$$3(SCN)_2 + 4H_2O \longrightarrow 5HSCN + HCN + H_2SO_4$$

Furthermore, thiocyanogen decomposes rapidly in the free state and it often explodes upon separation from solution. Upon standing, polymerization products separate from the solution which vary in color from yellow to red. The chemistry of this polymerization has been explained by the two intermediates, sulfur dicyanide and sulfur dithiocyanate.[19]

Free thiocyanogen can also be obtained either by the cautious oxidation of thiocyanic acid or by the interaction of thiocyanic acid and plumbic acetate in which the initial product, lead (IV) thiocyanate, decomposes at once into thiocyanogen and lead (II) thiocyanate.[19] The formation of thiocyanogen by electrolysis will be discussed later.

Bjerrum observed that the hydrolysis of thiocyanogen proceeds slowly in acid solution. This fact is important in the use of thiocyanogen for preparative purposes. Hydrolysis can be avoided completely if the thiocyanogen reacts first with another substance present in solution. The following reactions, which can be carried out volumetrically, serve as illustrations[20]:

$$(SCN)_2 + 2HI \longrightarrow 2HSCN + I_2$$

$$(SCN)_2 + 2Na_2S_2O_3 \longrightarrow 2NaSCN + Na_2S_4O_6$$

$$(SCN)_2 + H_2S \longrightarrow 2HSCN + S$$

The use of thiocyanogen in the volumetric analysis of organic compounds has been valuable.

1. Thiocyanation with Free Thiocyanogen in Solution

Söderbäck observed substitution reactions of preparative interest when aromatic compounds such as aniline, dimethylaniline, di- and triphenylamines, and phenol were treated with thiocyanogen:

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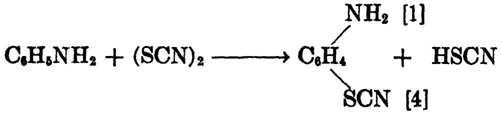
[16] Bjerrum and Kischner, *Die Rhodanide des Goldes und des freie Rhodan,* Verlag Horst, Copenhagen, 1918.

[17] Söderbäck, *Ann.,* 419, 217 (1919).

[18] Kaufmann and Kögler, *Ber.,* 59, 178 (1926).

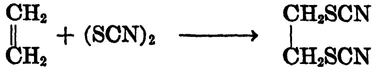
[19] Kaufmann, *Arch. Pharm.,* 263, 698 (1925).

[20] Kaufmann and Gärtner, *Ber.,* 57, 928 (1924).



$$C_6H_5NH_2 + (SCN)_2 \longrightarrow C_6H_4\begin{matrix}NH_2\ [1]\\ \\ SCN\ [4]\end{matrix} + HSCN$$

Kaufmann and Liepe[21] found that addition products were formed when unsaturated compounds were treated with free thiocyanogen:



$$\begin{matrix}CH_2\\ \| \\ CH_2\end{matrix} + (SCN)_2 \longrightarrow \begin{matrix}CH_2SCN\\ | \\ CH_2SCN\end{matrix}$$

The selective and partial addition to compounds containing several double bonds is the basis for the thiocyanometric determination of fats. Light has a considerable effect on these reactions which often lead to equilibrium. In the absence of light, thiocyanogen will add to the following compounds in a solution of glacial acetic acid and carbon tetrachloride: ethylene, butylene, phenylacetylene, tolan, anethole, safrole, allyl alcohol, oleic acid, elaidic acid, erucic acid, brassidic acid, ricinelaidic acid, acetoacetic ester, acetyldibenzoylmethane, ethyl α,β-diacetylsuccinate, formylphenylacetic ester, antipyrine, and pinene. No addition products were obtained from the following compounds under exactly the same conditions: acetylene, styrene, stilbene, crotonic acid, fumaric acid, maleic acid, cinnamic acid and its methyl ester, cinnamaldehyde, α_2,β- and α-diacetylsuccinic esters, stearic acid, and behenolic acid. The first three compounds, however, take up thiocyanogen upon irradiation, which illustrates the effect of light in this reaction.

The thiocyanogen solution is prepared as follows:

Pure lead thiocyanate, free of basic salts, is suspended in dry carbon tetrachloride or benzene, etc., and stirred with slightly less than the theoretical amount of bromine until the solution is decolorized. The lead bromide is filtered off through a dry filter along with the excess lead thiocyanate. The freshly prepared solution of thiocyanogen is water-clear when the reagents are pure and the containers are completely dry.

The compound to be thiocyanated is now added either in the pure form or in solution. The reaction is slow enough at room temperature so that a certain amount of polymerization of thiocyanogen cannot be avoided. The amount of polymerization is increased if the reaction is accelerated by the application of heat. Obviously, the yield is poor if the thiocyanation proceeds more slowly than the polymerization reaction. However, the thiocyanate is easily separated, because the polymer is insoluble in water and organic solvents.

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[21] Kaufmann and Liepe, *Arch. Pharm.*, **33**, 139 (1923).

Recently, thiocyanogen solutions have been prepared, which are stable for at least 8 days,[22] by treatment of a solution of bromine in a mixture of acetic acid and dry, redistilled carbon tetrachloride with a suspension of plumbous thiocyanate in carefully dried and redistilled acetic acid containing an excess of acetic anhydride.

Examples

(*a*) *Substitution*: *p-Thiocyanodimethylaniline.*[23] A solution of 1 mole of dimethylaniline in absolute ether is added dropwise to a solution of 1 mole of thiocyanogen in ether. A precipitate begins to form after about one-half of the amine solution has been added. This pale yellow material is a mixture of the product and polymeric thiocyanogen. The mixture is filtered and the filtrate is concentrated to dryness under reduced pressure, leaving colorless crystals of *p*-thiocyanodimethylaniline. The unreacted dimethylaniline is removed by two recrystallizations from alcohol; m.p. 73° to 74°C.

(*b*) *Addition*: *Dithiocyanoanethole.*[24] Anethole (2 g.) is dissolved in ether and treated with an ethereal solution containing 1.6 g. of thiocyanogen. After standing for 12 hours, the precipitate is collected in a Büchner funnel and recrystallized from ether. Yield, 3 g.; m.p. 87°C.

From the standpoint of chemical reactivity, thiocyanogen is much less active than bromine in the addition to organic compounds. This difference is illustrated in the case of dihydrocollidinedicarboxylic ester. 7 chlorine atoms, 4 bromine atoms, and 2 thiocyano groups add to this compound, while iodine does not react.[25] The addition of thiocyanogen can be accelerated by ferric thiocyanate which is formed when iron powder is added to the thiocyanogen solution.[25]

Numerous investigators have found applications for the addition of thiocyanogen to double bonds,[26] *e.g.*, thiocyanogen reacts with rubber,[27] isoprene,[28] butadiene,[29] and cyclohexene.[30] Furthermore, work has been done on the addition of thiocyanogen to fats and fatty acids[31] and the essential oils.[32] It is therefore noteworthy that a patent has recently been granted for the addition of thiocyanogen to terpenes, *e.g.*, pinene.[33] The thiocyanogen was formed from lead thiocyanate and bromine in glacial acetic acid, and the addition products, some of which are known in the literature, are to be used as insecticides and as intermediates in the preparation of other terpene derivatives.

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[22] Gardner and Weinberger, in *Inorganic Syntheses*, McGraw-Hill, New York, 1939, Vol. I, p. 84.

[23] Söderbäck, *Ann.*, **419**, 275 (1919).

[24] Kaufmann and Liepe, *Arch. Pharm.*, **33**, 147 (1923).

[25] Kaufmann and Thomas, *Ber.*, **56**, 2520 (1923).

[26] Kaufmann, German Patent, 404,175.

[27] Pummerer and Stärk, *Ber.*, **64**, 825 (1921).

[28] Bruson and Calvert, *J. Am. Chem. Soc.*, **50**, 1735 (1928).

[29] Müller and Freitag, *J. prakt. Chem.*, **146**, 58 (1938).

[30] Dermer and Dysinger, *J. Am. Chem. Soc.*, **61**, 750 (1939).

[31] Kaufmann, *Studien auf dem Fettgebiet*, Verlag Chemie, Berlin, 1935, p. 51.

[32] Kaufmann and Barich, *Arch. Pharm.*, **267**, 1249 (1929).

[33] U. S. Patent, 2,188,495 (Hercules Powder Co.).

2. Thiocyanation with Nascent Thiocyanogen

In the thiocyanation with nascent thiocyanogen, thiocyanates of heavy metals are treated with halogen (*e.g.*, lead thiocyanate with iodine) in the presence of the compound to be thiocyanated.[34] The thiocyanation proceeds more rapidly when nascent thiocyanogen is used, and this method is particularly suitable for compounds which react with difficulty. The method gained practical importance only when it was found that the thiocyanogen can be liberated from the dissolved inorganic thiocyanate with bromine or chlorine without simultaneously halogenating the organic compound.[35] This reaction was expanded in cooperation with I. G. Farbenindustrie and was applied to numerous compounds.[36] The reaction can be carried out in methyl alcohol and methyl acetate solutions which are saturated with sodium chloride or sodium bromide,[37] and even in aqueous solution.

Thiazoles are prepared by the thiocyanation of para-substituted aromatic amines in acid solution. This can be expected from the behavior of *o*-amino thiocyanates. Examples are found in various patents.[38] A few of the new compounds which have been prepared are 2-amino-6-ethoxybenzothiazole from *p*-phenetidine, 2-amino-6-carbethoxybenzothiazole from ethyl *p*-aminobenzoate, 2-amino-6-methylbenzothiazole from *p*-toluidine, 2-amino-6-thiocyanobenzothiazole from *p*-thiocyanoaniline, 2-amino-6-chlorobenzothiazole from *p*-chloroaniline, 2-amino-6-chloro-4-methylbenzothiazole from 4-chloro-*o*-toluidine, 2-amino-α-naphthothiazole from α-naphthylamine, and 2-amino-β-naphthothiazole from β-naphthylamine.

The use of nascent thiocyanogen in synthetic work has been valuable.[39] Primary aromatic amines with the para position free are thiocyanated by use of an alkali thiocyanate and halogen, whereupon an aminoarylmercapto compound is produced in turn by reduction of the thiocyano compound, and this is converted to the corresponding aminoarylthioglycolic acid with chloroacetic acid. Halogenarylthioglycolic acids can be prepared by replacing the amino group with a halogen. These halides serve as intermediates in the preparation of dyes.

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[34] Kaufmann and Liepe, *Arch. Pharm.*, 33, 139 (1923).

[35] Kaufmann and Oehring, *Ber.*, 59, 187 (1926); German Patent, 484,360; U. S. Patent, 1,790,097; British Patent, 257,619.

[36] French Patents, 35,025, 620,799; British Patents, 257,619, 295,295, 303,813; Swiss Patents, 122,990, 127,258, 141,451–5, 124,075; Italian Patent, 330,838; Czechoslovakian Patents, 30,984, 23,811, 32,358.

[37] German Patents, 491,225, 492,885 (supplementary to German Patent, 484,360), 493,025; Swiss Patent, 137,209; U. S. Patent, 1,765,678.

[38] Kaufmann and Schubert, U. S. Patents, 1,787,315, 1,787,316.

[39] German Patent, 495,879; British Patent, 299,327.

Nascent thiocyanogen has been utilized in numerous investigations. Two cases may be mentioned where nascent thiocyanogen is definitely superior to the free thiocyanogen solution. In their work on isoprene and dimethylbutadiene, Bruson and Calvert[40] could not obtain a crystalline product by use of the free thiocyanogen solution. However, the thiocyanation with nascent thiocyanogen worked smoothly to give good yields. The room was darkened to minimize polymerization. Pratesi obtained thiocyanopyrrole which was converted into other sulfur derivatives.[41]

The following examples give the experimental details of the reaction:

(*a*) *Substitution*: *Thiocyanothymol.*[42] 15 g. of thymol and 35 g. of $NaSCN \cdot 2H_2O$ are dissolved in 150 ml. of methanol saturated with sodium bromide. A solution of 20 g. (6.7 ml.) of bromine in 30 ml. of the same saturated methanol solution is added dropwise at room temperature with mechanical stirring. After standing for one-half hour, 6 to 8 volumes of water are added to the mixture. The product precipitates as an oil and crystallizes upon standing for 2 hours in an ice bath. The product is dried on a clay plate and recrystallized from ligroin with charcoal, yielding white crystals. Yield, 95%; m.p. 105°C.

(*b*) *Addition*: *Dithiocyanostyrene.*[43] A solution of 20 g. of sodium thiocyanate in 200 g. of acetic acid (96%) is added to a solution of 10 g. of styrene in 50 g. of acetic acid. The flask is placed in an ice bath and a solution of 1.6 g. of bromine in acetic acid is dropped into the mixture. After standing for a few minutes, the clear reaction mixture is poured into an equal volume of water. The product precipitates as an oil and soon becomes crystalline. The crude material is recrystallized from water; m.p. 101°C.

(*c*) *Conversion of a Thiocyanate into a Disulfide in Alkaline Solution*: *Bis-(1-phenyl-2,3-dimethyl-5-pyrazolonyl-4) Disulfide.*[44] 19 parts of antipyrine and 20 parts of sodium thiocyanate are dissolved in 300 parts of acetic acid. A solution of 16 parts of bromine in glacial acetic acid is dropped in slowly. The reaction mixture, which contains the 4-thiocyanoantipyrine, is diluted with an equal volume of water and then made slightly alkaline with a solution of sodium carbonate in water. After a short time the yellow disulfide crystallizes and is filtered, washed, and dried. Pure bis-(1-phenyl-2,3-dimethyl-5-pyrazolonyl-4) disulfide is obtained without further purification; m.p. 256°C. This reaction is suitable for a lecture demonstration.

(*d*) *Rearrangement of o-Amino Thiocyanates in Acid Solution*: *2-Amino-6-carbethoxybenzothiazole.*[45] A solution of 4.95 g. of ethyl *p*-aminobenzoate in 30 ml. of 96% acetic acid is added to a solution of 10 g. of sodium thiocyanate in 20 ml.

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[40] Bruson and Calvert, *J. Am. Chem. Soc.*, 50, 1735 (1928); German Patent, 484-360.

[41] Pratesi, *Atti accad. Lincei*, 16, 443 (1932).

[42] Kaufmann and Weber, *Arch. Pharm.*, 267, 201 (1929).

[43] U. S. Patent, 1,790,097.

[44] Kaufmann and Liepe, *Ber.*, 56, 2514 (1923).

[45] Kaufmann, Oehring, and Clauberg, *Arch. Pharm.*, 266, 215 (1928).

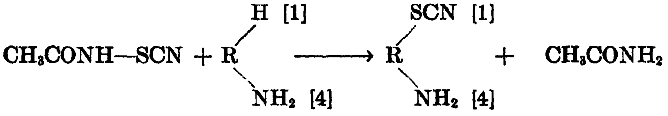
of acetic acid. This mixture is stirred vigorously while a solution of 1.7 ml. of bromine in acetic acid is added dropwise. The temperature is maintained at $-5\,°C.$ throughout the addition. The reaction mixture is boiled for one-half hour, stirred with charcoal, and filtered. The filtrate is diluted with water and neutralized with sodium carbonate. The precipitate is filtered off and recrystallized from dilute alcohol; m.p. 241 °C. The yield is almost quantitative.

There are numerous cases in which thiocyanogen will not react with organic compounds. For example, while aniline gives an excellent yield of *p*-thiocyanoaniline, acetanilide does not react.[46] This fact was confirmed by Brewster and Dains.[47] Furthermore, hydroxyl groups in certain positions can cause difficulty. Maschek[48] thiocyanated pyrocatechol, but hydroquinone, resorcinol, and phloroglucinol did not react. Consequently, no definite rule has yet been found to explain the thiocyanation of organic compounds, and each case must be treated individually.

3. Thiocyanation with Free Thiocyanogen Prepared from Inorganic Thiocyanates and Compounds Containing Labile Halogen

Compounds which split off a halogen easily will react with an inorganic thiocyanate to form thiocyanogen or unstable intermediates which act as thiocyanating agents. Spengler[49] prepared free thiocyanogen from sulfuryl chloride and lead thiocyanate in an inert solvent. The filtered solution containing the thiocyanogen was used as usual for preparative work. This method shows little advantage over the use of free halogen. The same applies for the use of ammonium thiocyanate and chloride of lime in acetic acid according to Zaboev and Kudryavtzev.[50] Neu[51] prepared thiocyanogen solutions from lead thiocyanate and aryl iodochlorides which were used for the preparation of organic compounds. Likhosherstov and Petrov[52] employed *N*-chloroamides such as chloroacetamide, dichlorourea, and dichloropentamethylenetetramine in the presence of ammonium thiocyanate in alcohol, acetic acid, and acetone solutions. The following equations show the proposed reaction of chloroacetamide.

$$CH_3CONHCl + NH_4SCN \longrightarrow NH_4Cl + CH_3CONH{-}SCN$$



$$CH_3CONH{-}SCN + \underset{NH_2\ [4]}{\overset{H\ [1]}{R}} \longrightarrow \underset{NH_2\ [4]}{\overset{SCN\ [1]}{R}} + CH_3CONH_2$$

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[46] Kaufmann and Weber, *Arch. Pharm.*, **267**, 197 (1929).

[47] Brewster and Dains, *J. Am. Chem. Soc.*, **58**, 1364 (1936).

[48] Maschek, *Monatsh.*, **63**, 216 (1933).

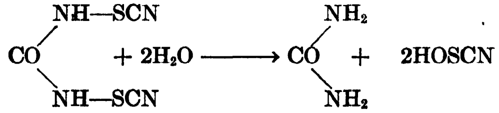
[49] Spengler, German Patent, 439,604; U. S. Patent, 1,594,697; British Patent, 240,420 (Agfa).

[50] Zaboev and Kudryavtzev, *J. Gen. Chem.* (*U. S. S. R.*), **5**, 1607 (1935).

[51] Neu, *Ber.*, **72**, 1505 (1939).

[52] Likhosherstov and Petrov, *J. Gen. Chem.* (*U. S. S. R.*), **3**, 183, 759 (1933); **5**, 981 (1935).

It was not learned from the report of the Russian work whether the formation of hypochlorite from the chloracetamide was excluded; neither was it learned whether unstable hypothiocyanic acid (HOSCN) was formed from $CH_3CONHSCN$ owing to small traces of water. The same applies to the reaction products from the interaction of dichlorourea and ammonium thiocyanate:



$$CO\begin{matrix}\diagup NH{-}SCN \\ \diagdown NH{-}SCN\end{matrix} + 2H_2O \longrightarrow CO\begin{matrix}\diagup NH_2 \\ \diagdown NH_2\end{matrix} + 2HOSCN$$

In analogy to the action of hypochlorite as a chlorinating agent, hypothiocyanic acid can act as a thiocyanating agent. The use of acid solutions is sometimes a disadvantage if the unstable thiocyanate is to be isolated. Likhosherstov and Petrov give an example of this. According to these authors dithiocyanobenzidine decomposes at 250°C., and Neu[53] reported that it did not decompose at 365°. However, Kaufmann and Büchmann found the melting point of dithiocyanobenzidine to be 160.5°. The first mentioned authors, working with acid solution, must have obtained the corresponding dithiazole derivative which decomposes above 300°C.

III. COPPER THIOCYANATE METHOD

According to the literature the conversion of black cupric thiocyanate into white cuprous thiocyanate proceeds as follows:

$$6Cu(SCN)_2 + 4H_2O \longrightarrow 6CuSCN + HCN + H_2SO_4 + 5HSCN$$

Considering the experience with plumbic thiocyanate, it might be assumed that free thiocyanogen, which immediately undergoes hydrolysis, is formed.

$$2Cu(SCN)_2 \rightleftharpoons 2CuSCN + (SCN)_2 \qquad (1)$$

$$3(SCN)_2 + 4H_2O \longrightarrow 5HSCN + HCN + H_2SO_4 \qquad (2)$$

The free thiocyanogen formed in accordance with Equation 1 could not be isolated for preparative purposes; however, by suitable methods it can be used as it is formed and thereupon offers a new method of thiocyanation called the copper thiocyanate method.[54] The reaction can be carried out in the absence of an organic solvent by conducting it in a slurry or paste or in aqueous solution. The procedure can be further simplified by use of a mixture of copper sulfate and sodium or ammonium thiocyanate in place of cupric thiocyanate. Also, the inorganic thiocyanate can be added to a mixture of the copper sulfate and the compound to be thiocyanated, or the copper sulfate can be stirred into a mixture of the thiocyanate and the organic compound. Each of the following reactions is accompanied by a color change from black to white owing to the formation of cuprous thiocyanate:

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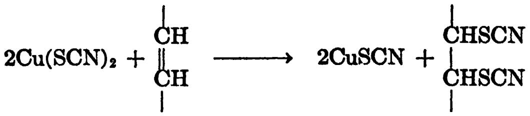
[53] Neu, *Ber.*, 72, 1505 (1939).

[54] Kaufmann and Küchler, *Ber.*, 67, 944 (1934); German Patent, 579,818.

$$2Cu(SCN)_2 + RH \longrightarrow 2CuSCN + RSCN + HSCN$$



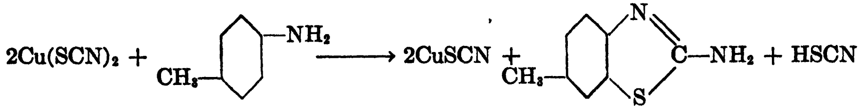
$$2Cu(SCN)_2 + \begin{matrix} | \\ CH \\ \| \\ CH \\ | \end{matrix} \longrightarrow 2CuSCN + \begin{matrix} | \\ CHSCN \\ | \\ CHSCN \\ | \end{matrix}$$

The cuprous thiocyanate can be recovered and used again. In certain cases (insecticides) the total reaction product can be used without further treatment. Finally, the copper thiocyanate method permits the end-product, *e.g.*, disulfide or thiazole, to be obtained without isolation of the organic thiocyanate. The method is illustrated by the following examples.[55]

(*1*) *1-Thiocyano-2-naphthylamine.* A solution of 7.1 parts of β-naphthylamine in 50 parts of ethyl acetate is treated with 20 parts of cupric thiocyanate with stirring. After decolorization occurs, the mixture is filtered, poured into water, separated from the ethyl acetate, and neutralized with sodium carbonate. The mixture is extracted with ether and the ether is removed. The residue contains 9.2 parts of 1-thiocyano-2-naphthylamine.

(*2*) *12,13-Dithiocyanobehenic Acid.* 25 parts of erucic acid in 180 parts of glacial acetic acid are warmed with 60 parts of cupric thiocyanate at 80°C. for a prolonged period. After filtration, the mixture is diluted with water and extracted with ether. The ether is removed and the residue is washed with ligroin. Yield, 20 parts of 12,13-dithiocyanobehenic acid.

(*3*) *2-Amino-6-methylbenzothiazole.* A solution of 2 g. of *p*-toluidine in 30 ml. of ethyl acetate is warmed gently with 7.0 g. of cupric thiocyanate with stirring until decolorization occurs. After the addition of hydrochloric acid, the acetate is removed. The residue is filtered and extracted several times with boiling water. The combined aqueous extracts are neutralized with ammonia and the product is filtered off. The yield of crude 2-amino-6-methylbenzothiazole is 2.5 g. When the product is recrystallized from dilute alcohol, a melting point of 134°C. is obtained.



Brewster and Dains[56] prepared several thiazoles by the cupric thiocyanate method. No thiocyanation occurred in compounds containing acetamido or carbethoxyamino groups. Monoalkylamines such as *N*-ethyl-*p*-toluidine and disubstituted amines such as 3-nitro-*p*-toluidine react in the normal manner.

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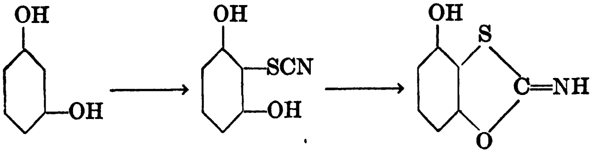
[55] German Patent, 579,818.

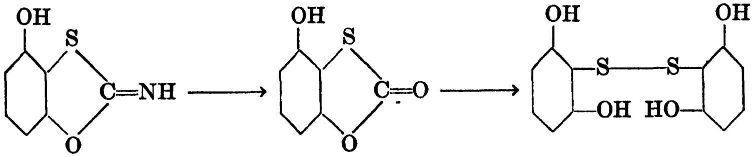
[56] Brewster and Dains, *J. Am. Chem. Soc.*, **58**, 1364 (1936).

The copper thiocyanate method is the subject of German Patent 579,818, and again of British Patent 513,473. According to the latter,[57] aniline and sodium thiocyanate in water or alcohol were treated with copper sulfate at 60°C. The *p*-thiocyanoaniline separated from hot water. Organic thiocyanates prepared in this manner were used in the preparation of dyes, as accelerators in vulcanization processes, and as insecticides.

According to French Patent 852,020, polyhydroxy compounds react with cupric thiocyanate to form thioxole derivatives.[58] The reaction results in the formation of the thiocyanate derivative which undergoes a ring closure, forming the iminothioxole compound. These compounds are called iminothiocarbonates in the French patent.



The copper thiocyanate method is distinctly superior to the alkali thiocyanate-halogen method (page 376) as far as the thiocyanation of polyhydroxy compounds is concerned. When the iminothioxole is heated with an acid, the imino group is replaced by oxygen. Saponification results in a ring cleavage with the formation of the disulfide of resorcinol.



IV. ELECTROLYTIC THIOCYANATION

It has already been mentioned that thiocyanogen can be formed by the electrolysis of inorganic thiocyanates. Kerstein and Hoffmann[59] observed that thiocyanogen produced in this manner reacts with acetone. Küchler and Kaufmann thiocyanated aniline, phenetidine, toluidines, and naphthylamines electrolytically in ethyl acetate, methanol, and also in a dilute sulfuric acid solution, using copper and carbon electrodes. Advantages of this method in contrast to the alkali thiocyanate-halogen method could not be observed.

In 1936 a patent was granted on the electrolytic thiocyanation of amino-4-hydroxyaryl compounds at temperatures below 5°C.,[60] but it was later rescinded.

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[57] British Patent, 513,473; *Chem. Zentr.*, 1940, I, 2066; *C.A.*, 35, 1804 (1941).
[58] French Patent, 852,020; *Chem. Zentr.*, 1940, II, 1360; *C.A.*, 36, 1951 (1942).
[59] Kerstein and Hoffmann, *Ber.*, 57, 491 (1924).

The corresponding French Patent 702,829 is noteworthy in that it claims rather good yields when copper cathodes and a rotating graphite anode are used. Fichter and Schönmann[61] followed the procedure of this patent. For example they obtained a 63% yield in the thiocyanation of dimethylaniline. When they increased the ammonium thiocyanate to 3 times the amount stated in the patent, the yield rose to 85%, with a utilization of 82.8% of the current. An electrolysis with 21.5 g. of dimethylaniline and 18.5 g. of ammonium thiocyanate with a current of 800 amperes per minute gave a crude yield of 20 g. (63.2%); with 37 g. of ammonium thiocyanate, the yield was 24 g. (75.9%). With 55.5 g. of ammonium thiocyanate 29.0 g. (91.7%) were obtained and no unchanged dimethylaniline could be detected. The crude product was almost pure. Pure *N*,*N*-dimethyl-4-thiocyanoaniline was obtained by dissolving this material in hydrochloric acid, precipitating the free base with ammonia, and recrystallizing from 90% alcohol. The current yield in these experiments was only 65%, because the current was applied in excess. If the ammonium thiocyanate concentration is trebled as compared with the patent, a yield of 85% of the product and a current yield of 82.8% are obtained. The yields of derivatives from diethylaniline and dimethyl-*p*-toluidine were also improved when the concentration of the thiocyanate ion was increased up to 4 times the calculated amount. Phenols such as guaiacol were also thiocyanated electrolytically by Fichter and Schönmann.[61] The following compounds could not be thiocyanated by this method: toluene, anisole, salicylic acid, methyl salicylate, and anethole.

The preceding compilation of methods for the thiocyanation of organic compounds shows that it is now possible to prepare organic thiocyanates in good yields by various procedures. The importance of the technical application of this reaction is somewhat dependent upon the cost of the necessary inorganic thiocyanates. The price of technical ammonium thiocyanate is now about 14 cents per pound. This price is higher than the estimate of Gluud and Klempt[62] who believe that ammonium thiocyanate in 30% solution might become available at a lower rate.

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[60] Patent Application, R31,130.

[61] Fichter and Schönmann, *Helv. Chim. Acta*, 19, 1411 (1936).

[62] Gluud and Klempt, *Angew. Chem.*, 40, 659 (1927).

The Diene Synthesis

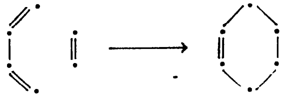
BY K. ALDER

Translated and revised by C. V. WILSON AND J. A. VANALLAN

I. LIMITS OF REACTION AND ITS PRACTICAL APPLICATION

Any attempt at a systematic treatment of the diene synthesis[1] must be strictly limited in its scope. In this review, therefore, only the application of the methods to the problem of preparative organic chemistry will be considered. The kinetics and stereochemistry of the reaction will be considered in so far as they are significant in analysis and determination of structure. Reactions, such as the formation of four-membered rings, which proceed with the displacement of hydrogen (substituting addition), and polymerizations and copolymerizations, which lead to high molecular weight compounds, will not be included, even though the use of dienes in such reactions has produced many significant results.

The general type of reaction, for which only simple combinations will be considered, can be represented as follows:



In reactions of this type there is no displacement of atoms, especially hydrogen atoms, and the products are, invariably, six-membered rings.

In order to comprehend the preparative significance of this general scheme it should be pointed out that the dots represent only multivalent atoms, in particular carbon, oxygen, and nitrogen atoms. Furthermore, two addenda are concerned in the reaction, a diene component with at least two conjugated double bonds (in general, multiple bonds) and a dienophile partner with at least one multiple bond.

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[1] References to the earlier literature include Alder, "Die Methoden der Diensynthese," in *Handbuch der biologischen Arbeitsmethoden*, Urban & Schwarzenberg, Berlin, 1933, Section 1, Part 2/II$_2$; Carleton Ellis, *The Chemistry of Synthetic Resins*, Reinhold, New York, 1935, Vol. II, p. 830; Delaby, "La Synthèse Dienique selon Diels et Alder," *Bull. soc. chim.*, **4**, 765 (1937). For general summaries, see Diels, *Angew. Chem.*, **42**, 911 (1929); *Ber.*, **69A**, 195 (1936); *Chem.-Ztg.*, **61**, 7 (1937); *Fortschritte der Chemie organischer Naturstoffe*, Springer, Vienna, 1939, Vol. III, p. 1. As a supplement to the present review the reader is referred to two more recent reviews on the subject; *viz.*, Norton, *Chem. Revs.*, **31**, 319 (1942) and Allen, *Chem. Revs.*, **37**, 209 (1945).

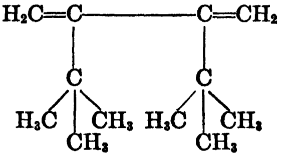
The case most thoroughly investigated, that in which all the atoms in the above representation are carbon atoms and in which a six-membered carbocyclic ring is formed, will be considered in detail. In addition, the formation of six-membered heterocyclic rings, which has been observed more recently, will be discussed.

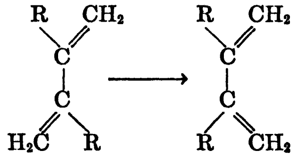
1. Diene Component

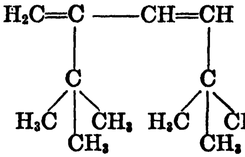
In discussing the diene component a general survey of the different types of compounds which are suited to the diene synthesis will be given.

The simplest members of the system $>C{=}C{-}C{=}C<$ are acyclic dienes, such as butadiene, $CH_2{=}CH{-}CH{=}CH_2$, its homologues, and its derivatives. Generally, they are excellent starting materials for the reaction. There are two prominent exceptions, both of which concern the role of substituents in conjugated systems.

While 1,2,3,4-tetramethylbutadiene, $CH_3CH{=}C(CH_3){-}C(CH_3){=}CHCH_3$, and 1,4-dimethyl-2,3-diethylbutadiene, $CH_3CH{=}C(C_2H_5){-}C(C_2H_5){=}CHCH_3$, add dienophiles easily,[2] 1,2,3,4-tetraphenylbutadiene, $C_6H_5CH{=}C(C_6H_5){-}C(C_6H_5){=}CHC_6H_5$,[3] and 2,3-di-*tert*-butylbutadiene (I)[4] do not.


(I)


(II) (III)


(IV)

Because of such differences a general rule has been formulated for the diene synthesis. According to this rule, the velocity of addition is dependent upon the number and kind of substituents in the diene as well as in the dienophile; high substitution slows down or completely inhibits the reaction.

The high degree of substitution prevents the reaction with tetraphenylbutadiene but with 2,3-di-*tert*-butylbutadiene a further point in connection with the influence of substituents is emphasized. Groups with large volumes in the 2,3 position can destroy completely the additive property of acyclic dienes. In all probability, large substituents on carbon atoms 2 and 3 hinder the formation of addition products by limiting the free rotation of the single bond (II and III). Further evidence for this conception lies in the fact that 1,3-di-*tert*-butylbutadiene (IV) undergoes a normal diene synthesis.[5]

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[2] Backer *et al.*, *Rec. trav. chim.*, **53**, 525 (1934); **58**, 761 (1939); **60**, 557 (1941).

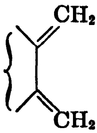
[3] Bergmann *et al.*, *Ann.*, **500**, 122 (1933); *J. Chem. Soc.*, **1939**, 391. Bergmann and Bergmann, *J. Am. Chem. Soc.*, **62**, 1699 (1940).

[4] Backer and Strating, *Rec. trav. chim.*, **58**, 643 (1939).

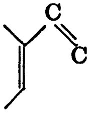
Phenyl groups in the 2,3 position do not exert the same effect as *tert*-butyl groups. A normal behavior is shown by 2,3-diphenylbutadiene (see page 416).

Since one of the first provisions necessary for an evaluation of the method is a knowledge of the influence of substituents on the course of the reaction, special emphasis is placed on just such information in Section II. There, additional evidence for the above generalization is also presented.

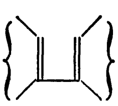
The second type of conjugated arrangement to be considered is that in which the double bonds are joined in a semicyclic manner to an alicyclic ring (V), form part of a ring (VI), or are contained in two rings (VII):



(V)

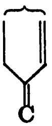


(VI)

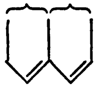


(VII)

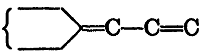
These groups are especially suited to the diene synthesis; in Section II several examples of additions to this type of diene will be discussed. For the present it is of interest to note that types VIII to X are exceptions:



(VIII)



(IX)



(X)

Compounds of types VIII and IX do not undergo the reaction, a fact that can be explained on general stereochemical grounds. Adducts which would be derived from them with dienophiles would contradict Bredt's law, which states that in bridged ring systems a double bond cannot exist at a bridge-head. The diene type (X) should lead to spirocyclic compounds. Its negative behavior cannot be ascribed to any general rule. The data available in this field are so limited that no comprehensive statement is possible.

Conjugated double bonds, one of which is part of an aromatic system, enter into the diene synthesis in a normal manner. Complex styrene derivatives in which the tendency toward polymerization is not so strongly pronounced as in the parent substance are valuable intermediates for the reaction. Styrene (XI), cyclohexenylnaphthalene (XII), and cyclopentenophenanthrene (XIII) represent these diene types. The addition takes place at the positions indicated. They will be considered individually in Section II:

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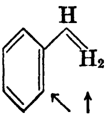
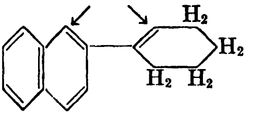
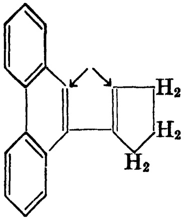
[5] Backer and Strating, *Rec. trav. chim.*, **56**, 1069 (1937). Favorsky and Nasarov, *Compt. rend.*, **196**, 1229 (1933); *Bull. soc. chim.*, **1**, 46 (1934); *Chem. Zentr.*, **1933, II**, 209; *Chem. Abstracts*, **27**, 3445 (1933).



(XI)

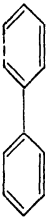


(XII)

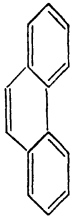


(XIII)

The question of whether or not two double bonds of conjugated aromatic systems will enter into a diene synthesis can (according to the modern conception) be answered as follows: The simple basic types like biphenyl (XIV) and phenanthrene (XV) are not susceptible to 1,4 addition of dienophiles, but in molecules like benzanthrene (XVI) and perylene (XVII) a concentration of condensed nuclei exerts the requisite effect to promote the addition, which takes place in the positions indicated (see p. 444 ff.).



(XIV)



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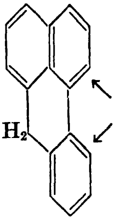

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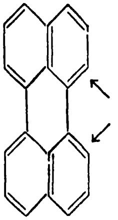
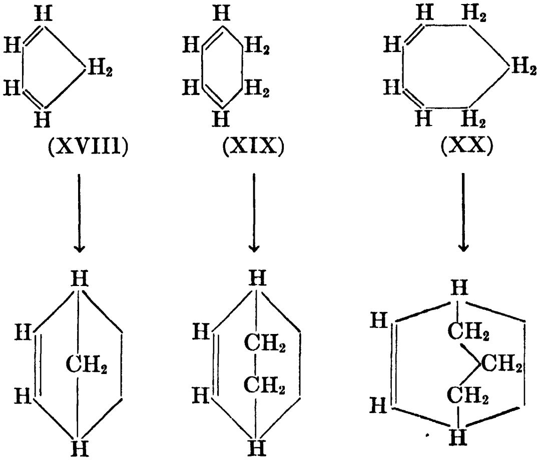


(XVII)

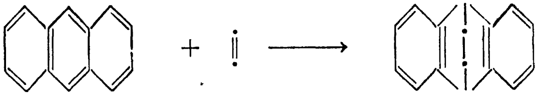
Finally, there are the mononuclear systems possessing conjugated double bonds. The research carried out in this field has been extraordinarily extensive. It includes alicyclic ring systems of various sizes, as well as aromatic and heterocyclic ring compounds.

To the first group belongs cyclopentadiene (XVIII), 1,3-cyclohexadiene (XIX), and 1,3-cycloheptadiene (XX). Because of their difficult accessibility, the behavior of dienes derived from larger rings has not been investigated (but compare the section on cyclooctatetrene, p. 507 ff.). Considerable research has been carried out with the cyclic dienes, as they are ideal components for the diene synthesis (see Section II). Complicated derivatives of these ring systems, such as exist in the cyclic terpenes, resin acids, steroids, and thebaine, add dienophiles very easily and form six-membered rings. All the additions proceed according to the general scheme previously proposed. Such systems as these, all of which contain *bridges*, will be considered fully in Section II of this review.



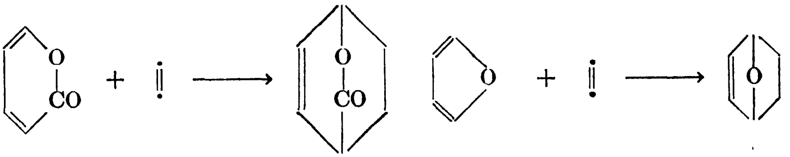
(XVIII) (XIX) (XX)

Aromatic compounds with at least three nuclei in a linear arrangement also function like 1,3-cyclohexadiene derivatives. The addition takes place at the double bond system of the central nucleus. Bridged ring systems (XXI) with distinctive properties result. These, too, will be considered in more detail in Section II.



(XXI)

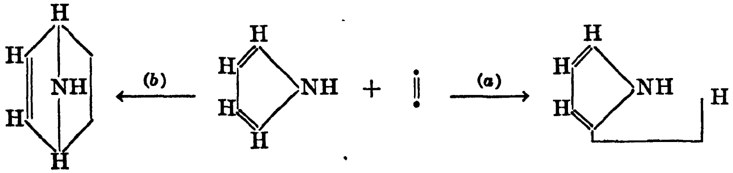
In the heterocyclic series the oxygen-containing coumalins (XXII) and furans (XXIV) show the diene behavior, *i.e.*, they add dienophile components in the 1,4 position to give bicyclic compounds with oxygen



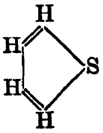
(XXII) (XXIII) (XXIV) (XXV)

bridges (XXIII and XXV).

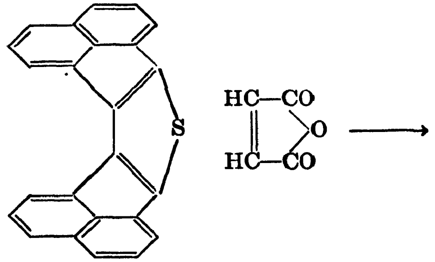
Individual cases which directly characterize this type of diene synthesis are recorded in Section II. It should be emphasized at this point that these systems lie on the border-line between true addition and "substituting addition." Furan, for example, shows a tendency to react with some dienophiles by the mechanism of substituting addition rather than by 1,4 addition. This form of reaction (*a*) is the rule with pyrrole. Diene syntheses (*b*) with this heterocycle have not been observed.[6]



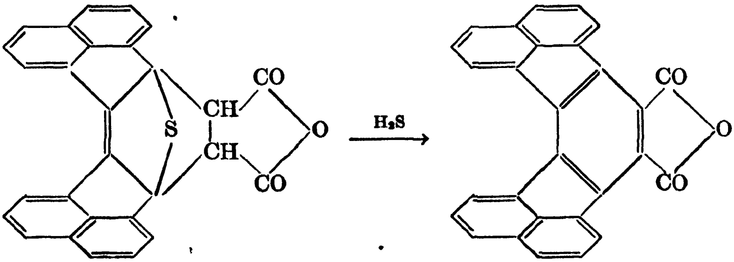
At this point the behavior of the thiophene group should be recorded. The well known similarity between thiophene (XXVI) and benzene is again demonstrated in the diene synthesis.



(XXVI)



(XXVII)



(XXVIII) (XXIX)

Neither compound shows any tendency to react with active dienophiles either by 1,4 addition or according to the substituting addition mechanism. As with the benzene system, where the more highly condensed types like anthracene and perylene show the character of dienes, thiophenes in which the molecule is more complex also show an increasing activity: 2,3,4,5-bis(1,8-naphthalene)thiophene (XXVII), for example, reacts easily with maleic anhydride. It is assumed that an addition product (XXVIII) is first formed and that this product loses hydrogen sulfide easily to give 3,4,5,6-bis(1,8-naphthalene)phthalic anhydride (XXIX).[7]

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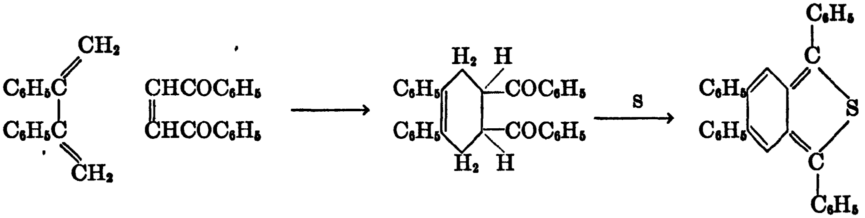
[6] *Cf.* Alder (foot-note 1), "Die Methoden der Diensynthese," p. 3171 ff.
[7] Clapp, *J. Am. Chem. Soc.*, 61, 2733 (1939).

The assumption that diene syntheses take place with certain thiophenes (see above) has been fully substantiated by the use of 1,3,5,6-tetraphenylisobenzothiophene (XXX).[8] This substance was prepared by treating the adduct from 2,3-diphenylbutadiene and dibenzoylethylene with sulfur.[8] It adds maleic anhydride to give 1,4,6,7-tetraphenyl-1,4-endothio-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylic anhydride (XXXI). The adduct dissociates into its components at its melting point (245°C.) and loses the bridge as H_2S by treatment with alcoholic hydrogen chloride. At the same time the anhydride is esterified but the resulting ester (XXXII) can be reconverted to the anhydride (XXXIII), by saponification followed by acidification. This is the first instance of the isolation of a substance containing a sulfur atom as a bridge across a six-membered ring.



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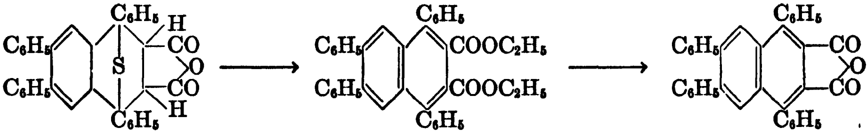
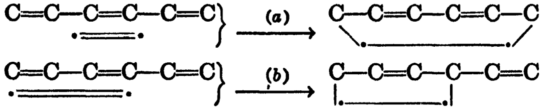


(XXXI) (XXXII) (XXXIII)

However, the use of thiophene compounds in the diene synthesis has not been sufficiently developed to warrant further consideration.

Another question arises when one turns from the dienes to tri-, tetra-, and pentaenes. Does the addition take place at the ends of the conjugated system (*a*), as has been observed for the addition of nascent hydrogen, or does it follow the general scheme of 1,4 addition (*b*), with the formation of a six-membered ring? All available evidence is clearly in favor of the latter possibility:



Such an abundance of research material is available for this group of dienes, that the tendency toward formation of six-membered rings must be considered as a general rule. Examples of addition reactions with this type of diene are dispersed throughout Section II. The various types are summarized below. The addition of dienophiles always takes place in the positions indicated:

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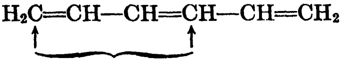
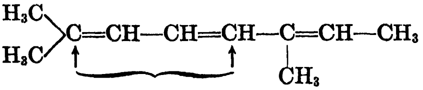
[8] Allen and Gates, *J. Am. Chem. Soc.*, 65, 1283 (1943).

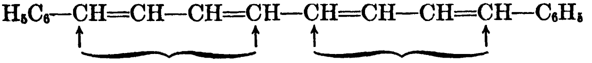


$$\underbrace{H_2\overset{}{C}{=}CH{-}CH{=}CH}{-}CH{=}CH_2$$

1,3,5-Hexatriene

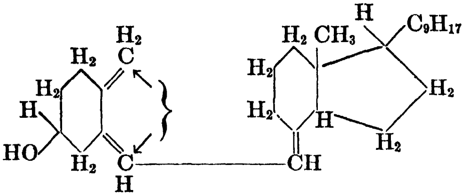


Alloocimene

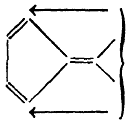


$$H_5C_6{-}\underbrace{CH{=}CH{-}CH{=}CH}{-}\underbrace{CH{=}CH{-}CH{=}CH}{-}C_6H_5$$

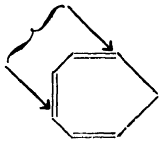
1,8-Diphenyloctatetraene



Vitamin D₂



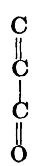
Fulvene



Cycloheptatriene

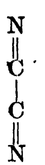
The point at which 1,4 addition takes place in tri- or polyene chains is dependent upon certain constitutional factors and the spatial arrangement of the double bonds. However, a six-membered ring results in every case.

Finally, some consideration should be given to the possibility of substituting for the diene component other compounds having the same bond structure as the diene, $\cdot{=}\cdot{-}\cdot{=}\cdot$, but in which 1 or more of the carbon atoms is replaced by some other atom or atoms. Little work has been done in this connection but it has been shown that the groups:



$$C{=}C{-}C{=}O$$

and



$$N{=}C{-}C{=}N$$

have the power to add dienophiles in the 1,4 position with the formation of heterocyclic six-membered rings (see pages 501 and 506).

On the other hand attempts to obtain corresponding reactions with benzalazine (XXXIV) (see page 506), cinnamilidineaniline (XXXV),[9] and benzalquinaldine (XXXVI)[9] were unsuccessful.

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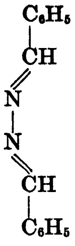
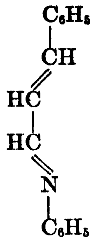
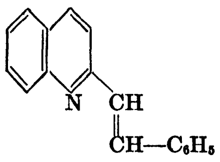
[9] Bergmann, *J. Am. Chem. Soc.*, **60**, 2811 (1938).



(XXXIV)

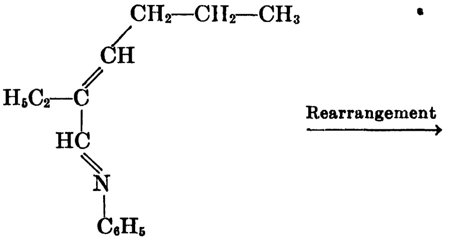


(XXXV)

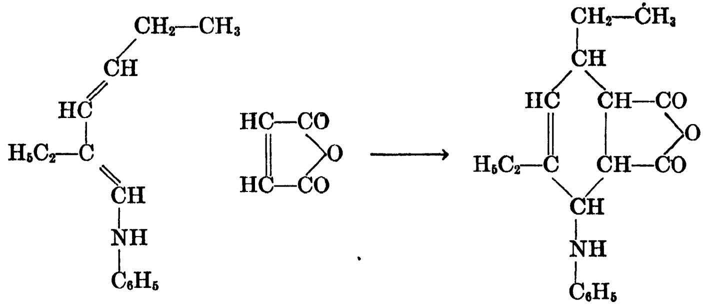


(XXXVI)

The addition of maleic anhydride to 2-ethyl-2-hexenalaniline[10] (XXXVII) is a characteristic example of the tendency to form carbocyclic six-membered rings. The addition does not take place to the $—N=C—C=C<$ system, but to the diene system (XXXVIII), which is formed from the anil by rearrangement, to give compound (XXXIX).



(XXXVII)



(XXXVIII) (XXXIX)

Similarly, maleic anhydride does not add to the $—N=C—C=N—$ system of 2,3-dimethylquinoxaline but to the $>C=C—C=C<$ system formed from the quinoxaline by rearrangement[11] (see page 397).

2. Enynes, Dienynes, and Ψ-Dienes as Diene Components

The types of components thus far discussed were dienes in the true sense of the word. However, recent observations indicate that the enynes with the characteristic conjugated double and triple bonds

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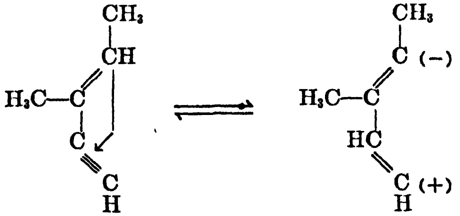
[10] Snyder, Hasbrouk, and Richardson, *J. Am. Chem. Soc.*, **61, 3558 (1940).**

[11] Schönberg and Mostafa, *J. Chem. Soc.*, **1943, 654.**

$$>C{=}C{-}C{\equiv}C{-}$$

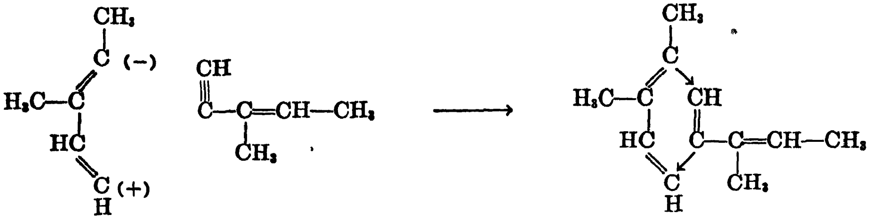
should be included in the conception of diene component.

The behavior of enynes in the diene synthesis is characterized by the fact that during the 1,4 addition a simultaneous rearrangement of hydrogen takes place. That this is true is clearly shown by the structure of the adduct. The following mechanism for this reaction is proposed because it can be applied to a number of apparently different processes: the enyne (XL) first changes into the tautomeric form (XLI), a zwitterion, which can add a dienophile with the formation of a six-membered ring.



(XL) (XLI)

The above example will serve to illustrate the mechanism. When heated, 3-methyl-3-pentene-1-yne (XL) changes into a benzenoid hydrocarbon (XLII).[12] It is probable that the zwitterion form (XLI) adds to the acetylenic compound, the normal form of the hydrocarbon.



(XLII)

This mechanism also explains the formation of 3,3,5-trimethylphthalide-7-carboxylic acid from 2,5-dimethyl-5-hexene-3-yne-2-ol and acetylenedicarboxylic acid.[13]

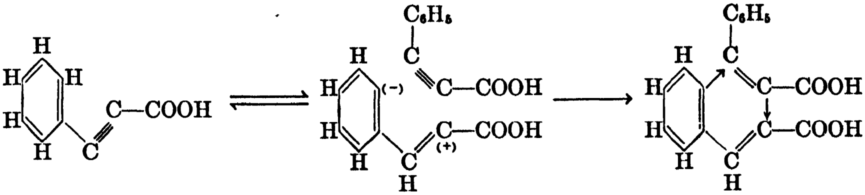
The formation of styrene from vinylacetylene can be explained in the same manner. In Section II other examples of the diene synthesis with enynes, $>C{=}C{-}C{\equiv}C{-}$, and dienynes, $>C{=}C{-}C{\equiv}C{-}C{=}C<$, which are in harmony with the above mechanism, will be considered.

---

[12] Favorsky and Sacharova, *J. Gen. Chem.* (*U. S. S. R.*), 7, 973 (1937); *Chem. Zentr.*, 1938,II, 1206; *Chem. Abstracts*, 31, 5318 (1937).

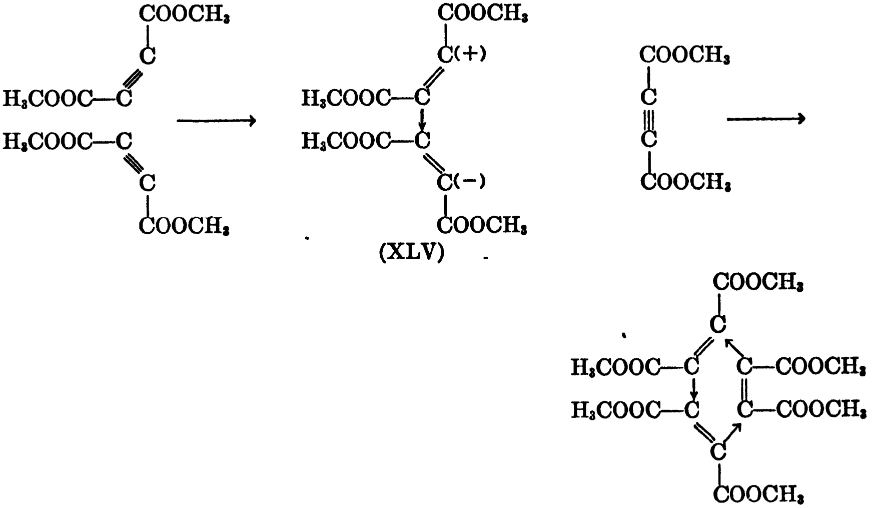
[13] Johnson, *J. Chem. Soc.*, 1945, 715.

It seems probable that the conversion of phenylpropiolic acid (XLIII) into the anhydride of 1-phenylnaphthalene-2,3-dicarboxylic acid (XLIV), by heating in acetic anhydride, is also a reaction of this type.[14] *o*-Methoxyphenylpropiolic acid dimerizes in the same manner.[15]



(XLIII) (XLIV)

The peculiar transformations of esters of acetylenedicarboxylic acid which have been described recently[16] are, without doubt, closely related to this phenomenon. The esters change with surprising ease into an ester of mellitic acid (XLVI). The reaction can be explained by assuming the primary formation of a zwitterion chain (XLV) from 2 molecules of the ester, followed by addition of a third ester molecule.



(XLV)

(XLVI)

The intermediate existence of zwitterions of this type (XLV) is clearly demonstrated by the fact that, under different reaction conditions, the >C═C— group will add with the formation of cyclic tertiary bases. In cases of this type it is even possible to isolate a *labile* adduct in which the ionic character of the chain (XLV) can be recognized. Naturally, the intermediate products will be converted to the stable six-membered ring. The formation of quinolizinetetracarboxylic ester (XLVIII) by the addition of acetylenedicarboxylic ester to pyridine illustrates this reaction. The intermediate labile adducts (XLVII) can be isolated.

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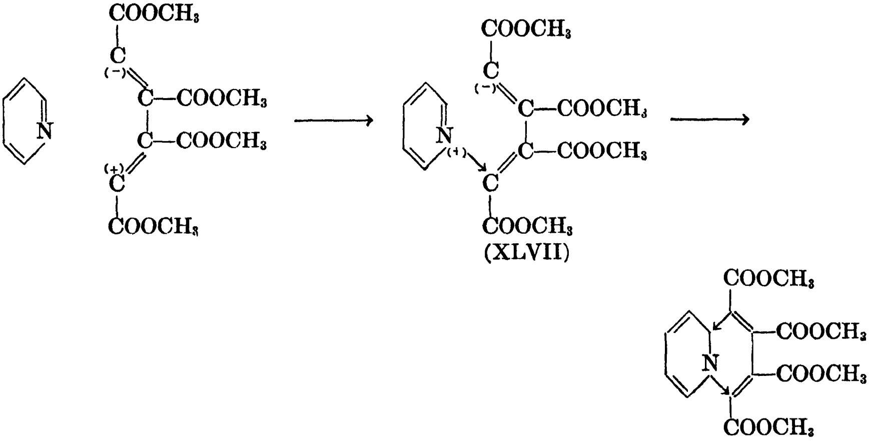
[14] Stobbe, *Ber.*, 40, 3372 (1907). Pfeiffer and Möller, *ibid.*, 40, 3839 (1907).

[15] Baddar, *J. Chem. Soc.*, 1947, 224.

[16] Diels and Alder, *Ann.*, 498, 16 (1932); 505, 103 (1933); 510, 87 (1934); see also the later works of Diels and co-workers. Diels and Koch, *Ann.*, 556, 41 (1944).

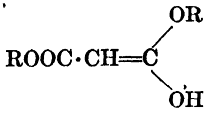


(XLVII)

(XLVIII)

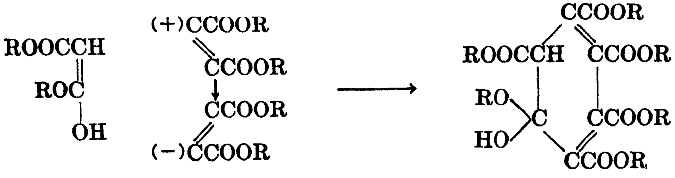
The method is of preparative significance for the synthesis of condensed heterocyclic ring systems in which the nitrogen atom is common to two rings.

More recently[17] it has been shown that 2 moles of acetylenedicarboxylic ester react with 1 mole of malonic ester in the presence of pyridine acetate to give a six-membered ring. The reaction apparently is a diene synthesis in which an enolic form of malonic ester:



$$\mathrm{ROOC{\cdot}CH{=}C}\begin{matrix}\diagup\mathrm{OR}\\ \diagdown\mathrm{OH}\end{matrix}$$

reacts as a dienophile with the zwitterion (XLIX) formed from 2 molecules



(XLIX)

(L)

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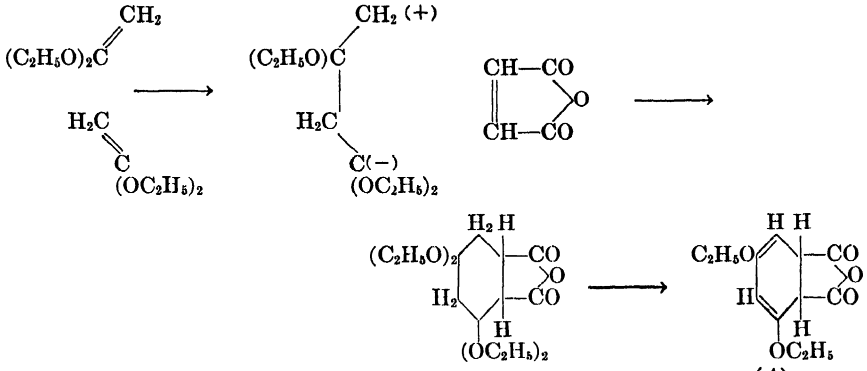
[17] Diels, *Ber.*, 75B, 1452 (1942).

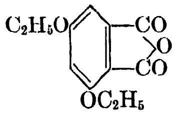
of acetylenedicarboxylic ester, to give compound L. This substance undergoes some interesting transformations but these are beyond the scope of this treatise.

When 4 moles of ketene acetal and 1 mole of maleic anhydride are mixed in ether solution, a 70% yield of 3,5-diethoxydihydrophthalic anhydride (*A*) results. If a 2:1 ratio of acetal to anhydride is used and the reaction is run in benzene, product *B* is formed.[18]

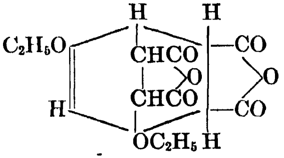
The translator [C. V. W.] suggests that this reaction involves an intermediate of the zwitterion type and takes the course shown in the accompanying diagram.



(*A*)



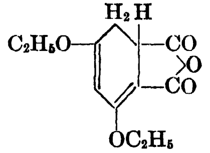
(*C*)



(*B*)

The dihydro derivative can be dehydrogenated with palladium to 3,5-diethoxyphthalic anhydride (*C*).

While McElvain and Cohen[18] give the dihydro compound the alternate structure (*A′*) in order to account for some of its properties, no similar instance of the



(*A′*)

addition of maleic anhydride across such a diene system has been described. From this point of view the bond system represented in (*A*) is to be preferred. The fact that dimethylmaleic anhydride will not add is inconclusive, for this dienophile adds with difficulty, if at all, to even the simplest diene.

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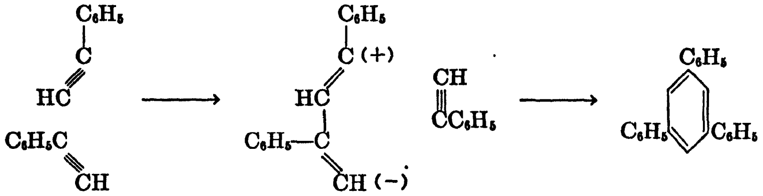
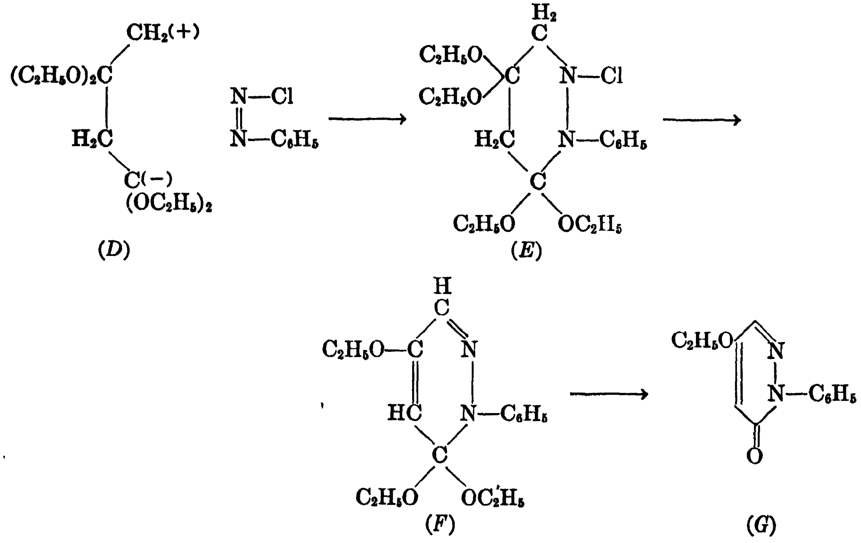
[18] McElvain and Cohen, *J. Am. Chem. Soc.*, **64**, 260 (1942).

The formation of 1,3,5-triphenylbenzene from phenylacetylene which is reported to take place quantitatively when the latter is heated at 260 °C. for 6 hours with a 33% aqueous solution of ethylamine[19] can be explained by a similar mechanism.



Furthermore, it is conceivable that the preparation of the pyridazone (*G*) from ketene acetal and benzenediazonium chloride[20] follows an analogous course. The acetal is assumed to form a zwitterion chain (*D*), which adds the diazonium salt to give the adduct (*E*). The latter loses hydrogen chloride and ethyl alcohol to form (*F*) and the acid acts on the acetal linkage to give the pyridazone, ethyl chloride, and ethyl alcohol.



This reaction also proceeds with *p*-ethoxy-, *p*-nitro-, and *p*-carbethoxyphenyldiazonium chlorides.

Finally, it seems probable that in the conversion of 1,4-naphthoquinone to triphthaloylbenzene (LI),[21] which is effected in the presence of pyridine and an oxidizing agent, intermediates similar to those depicted above for the enynes and acetylenic esters play an important role.

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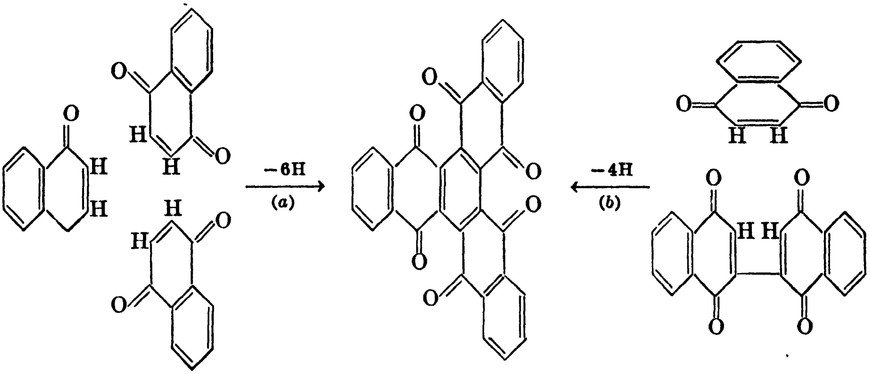
[19] Krussuski and Kiprijunov, *J. Russ. Phys. Chem. Soc.*, 56, 1 (1925); *Chem. Abstracts*, 19, 2817 (1926).

[20] McElvain and Jelenik, *J. Am. Chem. Soc.*, 65, 2236 (1943).

[21] Pummerer, Lüttringhaus, *et al.*, *Ber.*, 70, 2281 (1937); 71, 2569 (1938); 72, 1623 (1939).



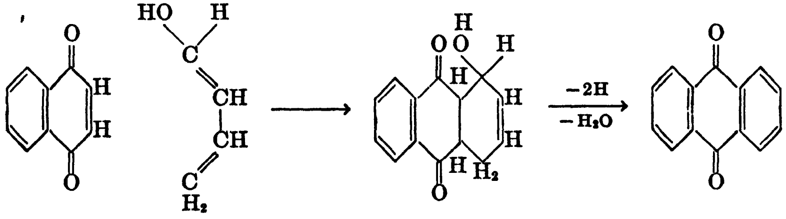
(LI) (LII)

The natural supposition is that 2,2′-dinaphthyl-1,4,1′,4′-diquinone (LII) is first formed, and that this reacts with a third molecule of α-naphthoquinone to form triphthaloylbenzene (LI), as represented by (*b*). However, this assumption does not completely explain the reaction. Triphthaloylbenzene (LI) is indeed formed from (LII) and α-naphthoquinone but much more slowly than from 1,4-naphthoquinone itself, as indicated in (*a*). Obviously, more active intermediate products than 2,2′-dinaphthyl-1,4,1′,4′-diquinone (LII) are concerned in the reaction.

The above examples indicate that future developments of these variations of the diene synthesis may lead to valuable preparative methods. However, since work in this field is still in a state of flux, only a few specific examples will be considered in Section II.

Some consideration should also be given to the class of compounds known as Ψ-dienes. Such compounds are normally stable substances which, under the conditions of the reaction, behave as dienes.

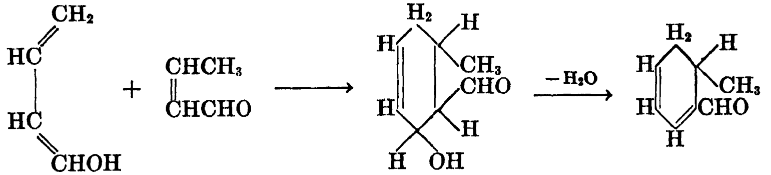
Thus, for example, crotonaldehyde and α-naphthoquinone react in benzene solution in the presence of piperidine to give anthraquinone (LV). Apparently crotonaldehyde acts as 1-hydroxybutadiene (LIII). The adduct (LIV) loses water and hydrogen easily to form anthraquinone.



(LIII) (LIV) (LV)

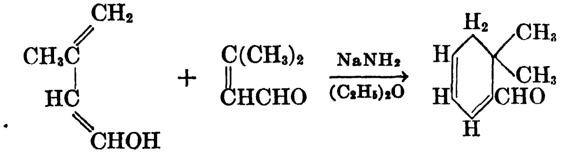
Crotonaldehyde and its derivatives, such as α-chloro- and α-methylcrotonaldehyde, applied to analogous syntheses[22] function as typical Ψ-dienes.

Crotonaldehyde also dimerizes in the presence of alkaline catalysts to give dihydro-*o*-tolualdehyde.[23] This can be formed as follows:



The reaction is analogous to the formation of anthraquinone from naphthoquinone and crotonaldehyde, and differs from the thermal dimerization of crotonaldehyde, which should lead to a pyran (*cf.* page 502).[24]

β-Methylcrotonaldehyde undergoes a similar dimerization in the presence of sodium amide to give 2,2,4-trimethyl-2,3-dihydrobenzaldehyde[25]:

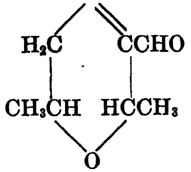


The action of benzalacetophenone with dypnone in the presence of sodium ethylate is also a reaction of this type.[26] The dypnone functions as a Ψ-diene:

[22] Nicodemus, Vollmann, and Schloffer, I. G. Farbenindustrie A.-G. (Patent Application 63,322); German Patent, 715,201; *Chem. Zentr.*, **1942,I,** 1811; *Chem. Abstracts*, **38,** 2049 (1944).

[23] Meerwein *et al.*, *J. prakt. Chem.*, **147,** 224 (1936). Bernhauer and Irrgang, *Ann.*, **525,** 48 (1936).

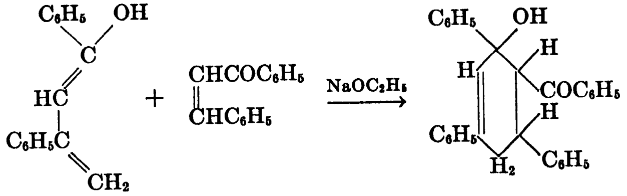
[24] A third dimer of crotonaldehyde is reported in the literature [Delepine *et al.*, *Compt. rend.*, **206,** 27 (1938); **212,** 1017 (1941); *Chem. Abstracts*, **32,** 2902 (1938); **38,** 2339 (1944); *Bull. soc. chim.*, **5,** 339 (1938); *Chem. Abstracts*, **32,** 4941 (1938)]. It is formed by the action of sulfuric acid on paraldehyde, and has the structure:



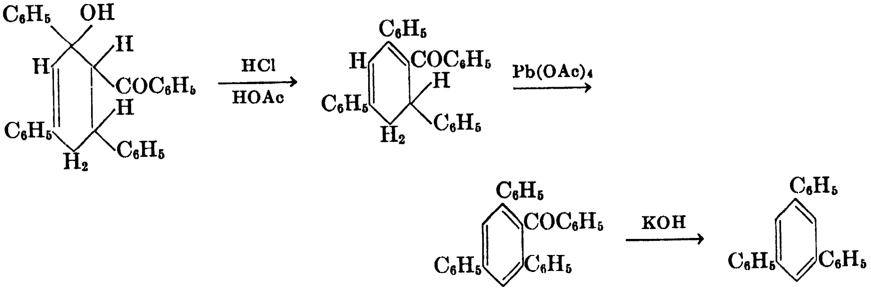
It will be noted that alkaline catalysts produce dihydrobenzene derivatives, while heat and acids lead to pyrans.

[25] Fischer and Lowenberg, *Ann.*, **494,** 263 (1932).

[26] Meerwein, *Ber.*, **77B,** 227 (1944). Ivanov and Ivanov, *Ber.*, **76,** 988, 1148 (1943); **77B,** 173, 180 (1944). Delacre, *Ann. chim.*, **2,** 82 (1914); *Chem. Abstracts*, **8,** 3420 (1914).

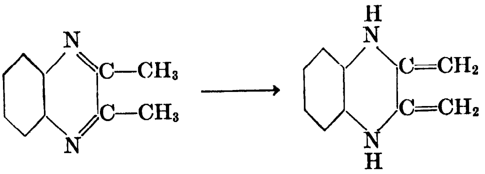


The structure of the 1,3,5-triphenyl-6-benzoyl-2-cyclohexene-1-ol thus formed is established by the following series of reactions:

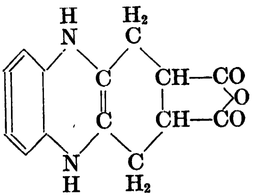


The dimerization of dypnone follows an analogous course, and the condensation of α-methyl-β-ethylacrolein with benzalacetophenone proceeds in a similar manner.

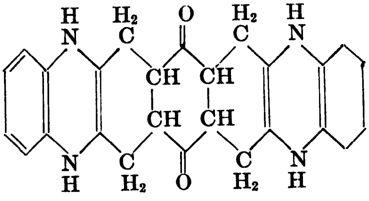
2,3-Dimethylquinoxaline represents a different type of Ψ-diene. This substance reacts with maleic anhydride and *p*-benzoquinone in toluene solution in a ratio of 1:1 with the former and 2:1 with the latter.[11] Presumably the compound rearranges to a diene, thus:



The diene now adds maleic anhydride or *p*-benzoquinone to give Compounds A and B, respectively. Evidence in support of this mechanism



Compound A

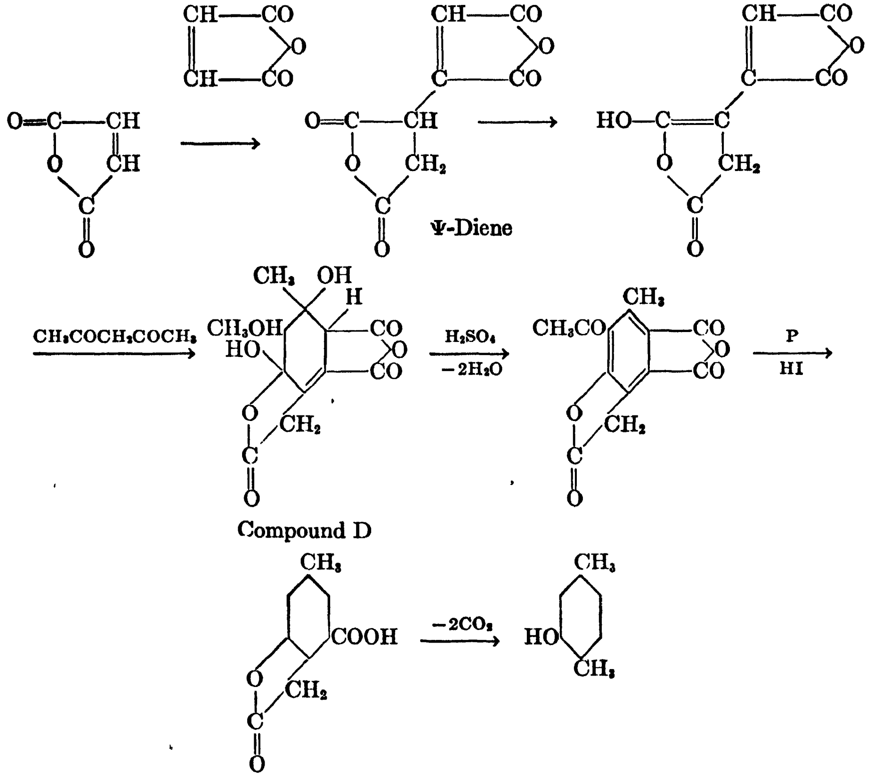


Compound B

arises from the fact that 2-methyl-, 2-phenyl-, 3-methyl-, or 2,3-diphenylquinoxaline does not react. Such compounds would not be capable of forming a diene system.

The reaction of acetylacetone with maleic anhydride is perhaps the most unusual reaction of the Ψ-diene type.[27] The adduct (D) formed from this pair of reactants consists of 2 moles of maleic anhydride and 1 of acetylacetone. This compound loses 2 moles of water on treatment with sulfuric acid; carbon dioxide and acetic acid on treatment with phosphorus and hydriodic acid; and 2 moles of carbon dioxide when decarboxylated, to give *p*-xylenol.

It has been suggested[27] that maleic anhydride dimerizes by the principle of substituting addition and that the dimer in the form of a diene adds the enolic form of acetylacetone. The compound (D) thus produced can explain the formation of *p*-xylenol when subjected to the reactions mentioned above. Acetoacetic ester reacts with maleic anhydride in the same manner.



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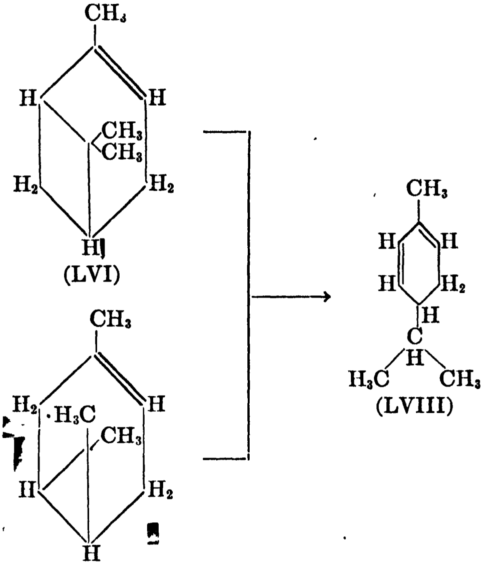
[27] Berner, *J. Chem. Soc.*, 1946, 1052.

Another group of Ψ-dienes consists of those compounds in which a double bond is conjugated with a labile ring. By ring opening such compounds can, under suitable conditions, form a second double bond, which creates the necessary conditions for a diene synthesis.

Diene syntheses with α-pinene (LVI) and β-carene (LVII) are characteristic cases of this type,[28] for these bicyclic olefins are first changed into the cyclic diene, α-phellandrene (LVIII).



(LVI) (LVII) (LVIII)

3. Dienophile Partner

As dienophile components compounds with a >C=C< or a —C≡C— linkage are the most common. However, the ability to add the diene is not confined to these multiple bond carbon compounds. The groups —N=C<, N≡C—, —N=N—, —N=O, and even the oxygen molecule, O=O, will add dienes in accordance with the general mechanism previously outlined.

Extensive experience has shown that all multiple bond compounds do not add at the same rate, but that the additive power depends to a high degree on the constitution of the compound.[29] α,β-Unsaturated carbonyl compounds add rapidly. They represent the most valuable components for synthetic processes. Typical examples of this group are acrolein (*a*), acrylic acid, $CH_2{=}CH{-}COOH$, maleic acid, $HOOC{-}CH{=}CH{-}COOH$, and its anhydride, *p*-quinone, and acetylenedicarboxylic acid, $HOOC{-}C{\equiv}C{-}COOH$. With these should be included the α,β-unsaturated nitriles, $>C{=}C{-}C{\equiv}N$, and the α,β-unsaturated nitro compounds (*b*).

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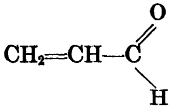
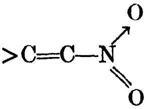
[28] Hultzsch, *Ber.*, **72**, 1178 (1939). *Cf.* also Arbuzov, *ibid.*, **67**, 563, 569, 1946 (1934); Lipp-Bredt-Savelsburg and Steinbrink, *J. prakt. Chem.*, **149**, 107 (1937).

[29] For a systematic survey of dienophile components, see Alder and Rickert, *Ann.*, **543**, 11 (1940).

(*a*)

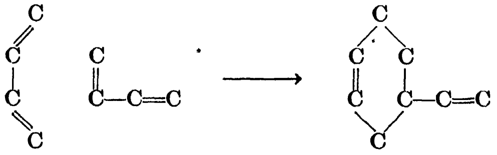




(*b*)

Dienophiles of this class (which will be considered fully in Section II) have a common characteristic. The additive combinations, $>C{=}C<$ and $-C{\equiv}C-$, are parts of conjugated systems, and the activating groups ($-CO$, $-CN$, $-NO_2$) possess a polar character. These two conditions certainly favor the addition of dienes, but they are not unconditionally necessary for the success of the reaction. This is demonstrated by the following class of dienophile components.

One of the double bonds in the system $>C{=}C{-}C{=}C<$ adds dienes with remarkable ease. In other words dienes can react as a diene and a dienophile simultaneously:



Many of the dimerizations which have been observed, especially those with simple compounds possessing conjugated double bonds, proceed as indicated above. Reactions of this type which are of preparative value or which have an adverse effect upon the course of a diene synthesis will be discussed later.

In contrast to the above, compounds like vinyl esters, $CH_2{=}CH{-}OCO{\cdot}R$, vinyl chloride, $CH_2{=}CHCl$, allyl alcohol, $CH_2{=}CH{-}CH_2OH$, vinylacetic acid, $CH_2{=}CH{-}CH_2COOH$, vinyl thio ethers, $CH_2{=}CH{-}SR$, and vinyl sulfones, $CH_2{=}CH{-}CSO_2R$, in which no conjugation exists, also act as dienophiles.[30] It is true that they add much more slowly than the α,β-unsaturated type, but their additive power is, nevertheless, sufficient for many reactions.

Furthermore, normal diene additions can be demonstrated for simple unsaturated hydrocarbons like propylene, $CH_3CH{=}CH_2$, and ethylene $CH_2{=}CH_2$, which are not conjugated and do not possess a polar group. In general these reactions proceed too slowly to acquire any preparative significance.[31]

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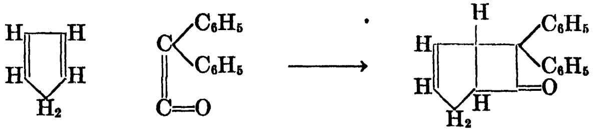
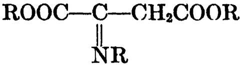
[30] Alder and Rickert, *Ann.*, **543,** 1 (1940). Alder, Rickert, and Windemuth, *Ber.*, **71,** 2451 (1938).

From the foregoing it is clear that most olefin and acetylene compounds function as dienophiles. However, ketene is a notable exception. The $>C{=}C<$ linkage in the system $>C{=}C{=}O$ does, indeed, add dienes but the additions are not diene syntheses. The resulting products are four-membered ring compounds[32]; for example:



It has not yet been established whether the $>C{=}C<$ linkage in the allenes, $>C{=}C{=}C<$, which resemble the ketenes in structure, possesses dienophile properties.

There is still another group of dienophiles. This group includes the compounds in which the unsaturated center consists of atoms other than carbon. The types known to date are the esters of azodicarboxylic acid, ROOC—N=N—COOR, the esters of iminosuccinic acid,



$$\mathrm{ROOC{-}\underset{\underset{NR}{\|}}{C}{-}CH_2COOR}$$

benzonitrile, $C_6H_5C{\equiv}N$, the esters of cyanoformic acid, $N{\equiv}C{-}COOR$, the nitroso compounds of the type of *p*-nitrosodimethylaniline, $O{=}N{-}C_6H_4{-}N(CH_3)_2$, and, finally, the oxygen molecule.

The first four types listed above will be treated more extensively later. The nitroso compounds and molecular oxygen will not be considered, since they are not yet sufficiently valuable for synthetic work. However, from the theoretical standpoint, reference should be made to molecular oxygen, because its ability to form peroxides, especially with cyclic dienes, is of outstanding interest.[33]

4. Practical Application of Diene Synthesis

It is a characteristic of the diene synthesis that it can be carried out very easily. If the reactivity of the components is not reduced too much by substituents, it is sufficient to bring them together in organic solvents in the calculated amounts. The reaction proceeds spontaneously with almost quantitative yields. Reactions in which heat is evolved should be carried out carefully, especially when large amounts of ingredients are used.[34] Under certain circumstances it is advantageous to work in aqueous emulsion,[35] if necessary, in the presence of capillary-active substances like alkyl-1-naphthalenesulfonic acids, sulfuric acid esters of higher fatty alcohols, or taurides of higher fatty acids; the dispersing action of such compounds assists materially in bringing about the reaction.

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[31] Joshel and Butz, *J. Am. Chem. Soc.*, **63**, 3350 (1941).

[32] For literature on this subject, see Alder and Rickert, *Ann.*, **543**, 15 (1940).

[33] Compare with this, the latest classification of Bergmann and McLean, *Chem. Revs.*, **28**, 367 (1941).

For sluggish reactions, heating the components under pressure, with or without solvents, usually leads to the desired result. If the stability and volatility of the components permit, their combination can be brought about by fusion.

However, certain limitations are imposed upon the use of higher temperatures for accelerating the reaction. The diene synthesis is a reversible reaction and the product often shows an appreciable cleavage even at fairly low temperatures. An equilibrium results and, because of the exothermic character of the addition, application of heat (amount required depends upon the size of the addends) (see p. 485 ff.) tends to decompose the addition product; *i.e.*, the equilibrium is shifted to the left (Le Châtelier's principle). In such cases it is advantageous to employ one of the two components in large excess, and to work with solvents from which the adduct will separate. In many cases the immediate alteration of the product by chemical means (*e.g.*, by dehydrogenation) makes the reaction of preparative value (see Section II).

Frequently nitrobenzene is a useful solvent because of its dehydrogenating action (pp. 444, 458). However, it has been suggested that its action is limited to adducts in which double ortho enolization is possible. Thus, adducts with maleic anhydride and quinones are dehydrogenated in nitrobenzene, while those from cinnamic or crotonic acids are not.[36] On the other hand, indene (LX) adds to methyleneanthrone (LIX) to give an adduct (LXI) which is dehydrogenated in nitrobenzene to an indenobenzanthrone (LXII).[37] This, together with the work of Clar,[38] indicates that the conditions suggested above are not necessary and that the determining factor may be the tendency toward formation of a stable ring system.

Recently[39] chloromaleic anhydride has found application in this connection. Isosafrole (LXIII) (and isoeugenol) adds this dienophile in

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[34] Diene syntheses are exothermic reactions. The heat of reaction is about 17 to 19 kilogram calories per mole.

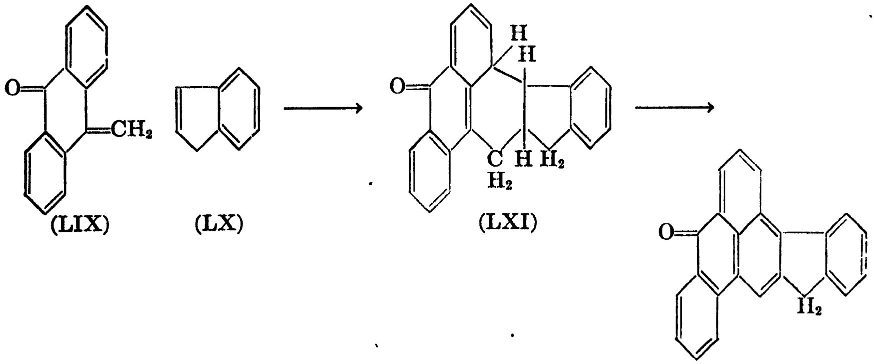
[35] Diels and Alder, *Ann.*, **490,** 247 (1931); I. G. Farbenindustrie A.-G., French Patent, 861,668. Wingfoot Corp., U. S. Patents, 2,217,632, 2,222,357; I. G. Farbenindustrie, A.-G., German Patent 710,131; *Chem. Abstracts*, **37,** 3453 (1943).

[36] Bergmann *et al.*, *J. Am. Chem. Soc.*, **60,** 1331 (1938); **64,** 176 (1942); *J. Org. Chem.*, **7,** 303 (1942).

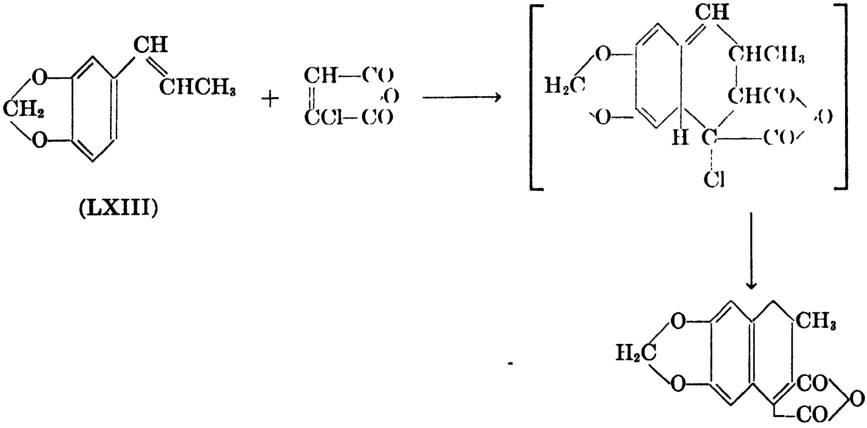
[37] Swain and Todd, *J. Chem. Soc.*, **1942,** 626.

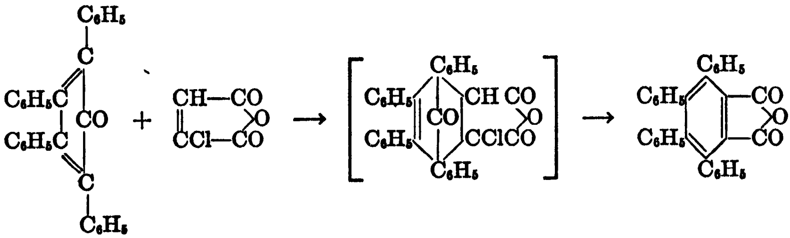
[38] Clar, *Ber.*, **69,** 1686 (1936).

[39] Synerholm, *J. Am. Chem. Soc.*, **67,** 345, 1229 (1945). Hudson and Robinson, *J. Chem. Soc.*, **1941,** 715.


(LIX) (LX) (LXI) (LXII)

xylene solution with simultaneous dehydrohalogenation to give a 3,4-dihydronaphthalene derivative (LXIV). Tetraphenylcyclopentadienone (LXV) (see p. 458 ff.) also adds chloromaleic anhydride in boiling bromobenzene; the adduct loses carbon monoxide and dehydrohalogenates under the conditions of the reaction to give tetraphenylphthalic anhydride (LXVI).


(LXIII) (LXIV)


(LXV) (LXVI)

This loss of hydrogen chloride under the conditions of the reaction gives chloromaleic anhydride an advantage over maleic anhydride. While the former leads to tetraphenylphthalic anhydride directly even if used in excess, the latter frequently adds to the diene system resulting from the loss of carbon monoxide from the original adduct (page 461).

The necessity of working at low temperatures for certain reactions suggests the use of catalysts to accelerate the addition. Very few data are available on this subject, but trichloroacetic acid[40] and trimethylamine[41] have been suggested as useful compounds for this purpose. In general, the influence of catalysts is small[42] and it appears that the presence of special condensing agents is, for the most part, superfluous.

Many of the dienes used, especially the simple types, tend to polymerize easily, either alone or with a dienophile, to form polymers or copolymers of high molecular weight. It is advantageous to suppress this undesirable, concurrent reaction, if possible, by the addition of suitable inhibitors (amines, phenols, copper salts, elementary copper, etc.). The formation of dimeric dienes, obviously, is not influenced by such additions, for these reactions are actually diene syntheses, which, in contrast to the chain reactions (polymerizations) mentioned above, are not sensitive to catalysts.

In general, as has been previously stated, the diene synthesis is an easily accomplished operation which entails no difficulty.

II. TYPES OF COMPOUNDS OBTAINABLE BY DIENE SYNTHESIS

1. Carbocyclic Ring Systems

A. Mononuclear Ring Systems

Simple mononuclear hydroaromatic compounds are produced in the diene synthesis when both components, diene and dienophile, belong to the aliphatic series. Various derivatives of cyclohexene and cyclohexadiene are formed, depending on the type of functional group present in either of the components. Thus, hydrocarbons, alcohols, ethers, aldehydes, ketones, acids, and polyfunctional compounds may be obtained by the diene synthesis.

The data are now so extensive that it is not practical for the purpose of this article to make a comprehensive survey of all available facts. The scope and value of the synthesis will be illustrated by some characteristic examples. In so far as the diene component is concerned, it is to be understood that almost all compounds which are homologous and analogous to the parent hydrocarbon of the series (*i.e.*, to butadiene, $CH_2{=}CH{-}CH{=}CH_2$) can be used in this synthesis. Some of them are contained in the following table[43]:

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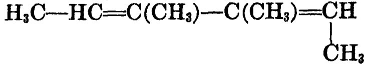
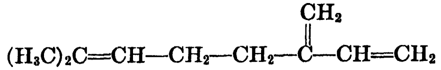
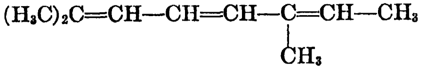
[40] Wassermann, French Patent, 838,454; *Chem. Abstracts*, **33**, 7818 (1939).

[41] Albrecht, *Ann.*, **348**, 45 (1906).

[42] Wassermann, *J. Chem. Soc.*, **1935**, 832; **1942**, 612, 618.

1-Methylbutadiene	$H_3C{-}HC{=}CH{-}CH{=}CH_2$
2-Methylbutadiene	$H_2C{=}C(CH_3){-}CH{=}CH_2$
1,1-Dimethylbutadiene[44]	$(H_3C)_2C{=}CH{-}CH{=}CH_2$
1,2-Dimethylbutadiene[45]	$H_3C{-}HC{=}C(CH_3){-}CH{=}CH_2$
1,3-Dimethylbutadiene	$H_3C{-}HC{=}CH{-}C(CH_3){=}CH_2$
1,4-Dimethylbutadiene	$H_3C{-}HC{=}CH{-}CH{=}CH{-}CH_3$
2,3-Dimethylbutadiene	$H_2C{=}C(CH_3){-}C(CH_3){=}CH_2$
1,1,3-Trimethylbutadiene	$(H_3C)_2C{=}CH{-}C(CH_3){=}CH_2$
1,2,3,4-Tetramethylbutadiene[46]	 $H_3C{-}HC{=}C(CH_3){-}C(CH_3){=}\underset{\displaystyle CH_3}{\underset{\vert}{C}H}$

The acyclic terpene hydrocarbons belong to the same class of reactive acyclic dienes:

Myrcene[47,48]	 $(H_3C)_2C{=}CH{-}CH_2{-}CH_2{-}\overset{\displaystyle CH_2}{\overset{\Vert}{C}}{-}CH{=}CH_2$
Alloocimene[49]	 $(H_3C)_2C{=}CH{-}CH{=}CH{-}\underset{\displaystyle CH_3}{\underset{\vert}{C}}{=}CH{-}CH_3$

From the large amount of material which has been presented in Section I and from that which follows, it is obvious that the scope of the diene synthesis is rather wide. However, in the case of those butadiene hydrocarbons which possess large substituents in the 2,3 position, the reactivity toward dienophiles is, to a large extent, lost. The case of 2,3 di-*tert*-butyl-1,3-butadiene, $H_2C{=}C(t\text{-}C_4H_9){-}(t\text{-}C_4H_9)C{=}CH_2$, has already been discussed (see page 382).

Mention was also made of the behavior of trienes with three conjugated double bonds. The rule which was formulated states that when 1,4 and 1,6 addition is possible, the former takes place preferentially; thus, six-membered and not eight-membered rings are always formed.[50-52]

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[43] Compare the review of Alder (foot-note 1). In this section the information from the earlier publication has been revised and enlarged by further examples from the literature.

[44] Slobodin, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 241 (1939); *Chem. Zentr.*, **1939, II**, 65.

[45] Brunner *et al.*, *Monatsh.*, **63**, 79 (1933). Farmer and Warren, *J. Chem. Soc.*, **1931**, 3235. Fieser and Webber, *J. Am. Chem. Soc.*, **62**, 1360 (1940).

[46] Backer *et al.*, *Rec. trav. chim.*, **58**, 761 (1939); **60**, 557 (1941).

[47] Diels and Alder, *Ann.*, **470**, 62 (1929).

[48] Ruzicka, *Helv. Chim. Acta*, **19**, 419 (1936).

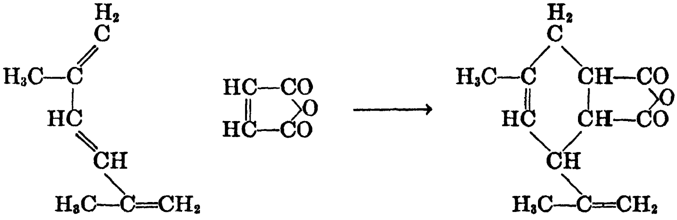
[49] Arbuzov, *Ber.*, **87**, 563, 569, 1946 (1934).

[50] Farmer and Warren, *J. Chem. Soc.*, **1929**, 908; I. G. Farbenindustrie A.-G., Swiss Patents 143,242–143,257, inclusive; *Chem. Zentr.*, **1931, I**, 2938. Butz, *et al.*, *J. Org. Chem.*, **5**, 171 (1940). Kipping and Wild, *J. Chem. Soc.*, **1940**, 1239. Compare the above diene synthesis of alloocimene (Arbuzov, *loc. cit.* 49) and the addition of the three-fold unsaturated higher fatty acids (see p. 412).

[51] Butz *et al.*, *J. Am. Chem. Soc.*, **60**, 216 (1938).

[52] Kharasch *et al.*, *J. Am. Chem. Soc.*, **62**, 2034 (1940).

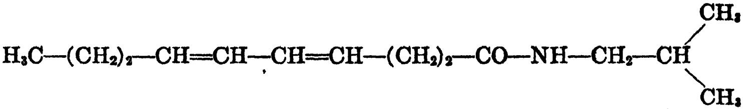
This rule has been completely confirmed in the case of alicylic trienes. An example of such a case is found in the addition of maleic anhydride to 2,5-dimethyl-1,3,5-hexatriene (LXVII), which leads to 3-isopropenyl-5-methyl-1,2,3,6-tetrahydrophthalic acid (LXVIII).[52]


(LXVII) (LXVIII)

In addition to these hydrocarbons numerous other derivatives of butadiene have been found to be of use in the diene synthesis. From this series the following examples may be mentioned:

Chloroprene[53]	$H_2C{=}CH{-}CCl{=}CH_2$
Bromoprene[54]	$H_2C{=}CH{-}CBr{=}CH_2$
1-Acetoxybutadiene[55]	$H_2C{=}CH{-}CH{=}CH{-}OCOCH_3$
2-Acetoxybutadiene[56,57]	$H_2C{=}CH{-}C(OCOCH_3){=}CH_2$
1-Alkoxybutadiene[58,59]	$H_2C{=}CH{-}CH{=}CH{-}OR$
Sorbic acid[47,53,60]	$H_3C{-}CH{=}CH{-}CH{=}CH{-}COOH$
Muconic acid[61,62]	$HOOC{-}CH{=}CH{-}CH{=}CH{-}COOH$
1-Diethylaminobutadiene[62] 2-Alkoxybutadiene[59]	$(C_2H_5)_2NCH{=}CH{-}CH{=}CH_2$

To complete this group such naturally occurring substances as spilanthol[63]:



$$H_3C{-}(CH_2)_2{-}CH{=}CH{-}CH{=}CH{-}(CH_2)_2{-}CO{-}NH{-}CH_2{-}CH(CH_3)_2$$

the acrid principle of garden cress, and the highly unsaturated fatty acids of the type of eleostearic and licanic acid, which will be mentioned later, should be added.

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[53] Carothers *et al.*, *J. Am. Chem. Soc.*, **53**, 4203 (1931); **54**, 4071 (1932); **55**, 1624, 2813 (1933).

[54] Carothers *et al.*, *J. Am. Chem. Soc.*, **55**, 786 (1933).

[55] Wacker (to Gesellschaft für electrochemische Industrie G.M.b.H.) British Patent, 493,196; *Chem. Zentr.*, **1939,I**, 796; *Chem. Abstracts*, **33**, 1758 (1939).

[56] Werntz, *J. Am. Chem. Soc.*, **57**, 204 (1935).

[57] Wacker, Italian Patent, 365,852; *Chem. Zentr.*, **1940,I**, 465.

[58] Wichterle, *Collection Czechoslov. Chem. Commun.*, **10**, 493 (1938); *Chem. Zentr.*, **1939,II**, 1466. See also *Chem. Abstracts*, **33**, 1659 (1939).

[59] Dykstra, *J. Am. Chem. Soc.*, **57**, 2255 (1935). Fiesselmann, *Ber.*, **75B**, 881 (1942).

[60] Wagner-Jauregg and Helmert, *Ber.*, **71**, 2535 (1938).

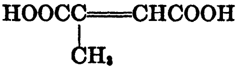
[61] Farmer and Warren, *J. Chem. Soc.*, **1929**, 904. I. G. Farbenindustrie A.-G. Swiss Patents, 143,242–143,257, inclusive; *Chem. Zentr.*, **1931, I**, 2938

[62] Langenbeck *et al.*, *Ber.*, **75B**, 232 (1942).

[63] Asano and Kanematsu, *Ber.*, **65**, 1602 (1932).

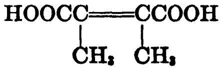
The diene component having thus been briefly considered, the dienophile will be discussed next. There is just as large a variety.[64] The α,β-carbonyl compounds such as aldehydes, ketones, acids, and esters are the most important. Such compounds are illustrated by acrolein, $CH_2{=}CHCHO$, crotonaldehyde, $CH_3CH{=}CHCHO$, vinyl methyl ketone, $CH_2{=}CHCOCH_3$, ethylideneacetone, $CH_3CH{=}CHCOCH_3$, acrylic acid, $CH_2{=}CHCOOH$, and crotonic acid, $CH_3CH{=}CHCOOH$.

In the polybasic, unsaturated acid series maleic acid, $HOOCCH{=}CHCOOH$, and its anhydride, because of their reactivity and frequent use as dienophiles, are undoubtedly the most important. However, its homologues, especially citraconic acid (*a*), pyrocinchonic acid (*b*), and itaconic acid (*c*), have considerable value for synthetic work. Methylenemalonic acid (*d*), and methyleneacetoacetic acid (*e*), have recently been added as dienophiles to this series of α,β-unsaturated carbonyl compounds.[65,66] The highly substituted ethylenetetracarboxylic acid (*f*), completes this series.



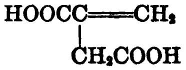
$HOOC\underset{\substack{| \\ CH_3}}{C}{=}CHCOOH$

(*a*)



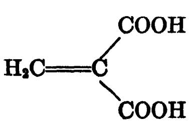
$HOOC\underset{\substack{| \\ CH_3}}{C}{=}\underset{\substack{| \\ CH_3}}{C}COOH$

(*b*)

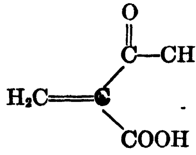


$HOOC\underset{\substack{| \\ CH_2COOH}}{C}{=}CH_2$

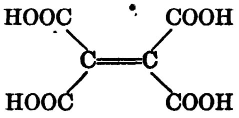
(*c*)



(*d*)



(*e*)



(*f*)

In the acetylene series, propiolic, $HC{\equiv}CCOOH$, and acetylenedicarboxylic acids, $HOOCC{\equiv}CCOOH$, have received the most attention.

In place of the free acids, of course, the anhydride, ester, amide, imide, and nitrile may be used. Use of the acid chloride sometimes shows decided advantages over the free acid and should be referred to for comparison.[60,67] Dibenzoylacetylene, $C_6H_5COC{\equiv}CCOC_6H_5$,[68] and butynone, $CH{\equiv}CCOCH_3$,[69] also react with simple dienes.

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[64] Compare Alder (foot-note 1), "Die Methoden der Diensynthese," p. 3105 ff.

[65] Alder and Rickert, *Ber.*, 72, 1983 (1939).

[66] Bachman and Tanner, *J. Org. Chem.*, 4, 493 (1939); U. S. Patent, 2,212,506.

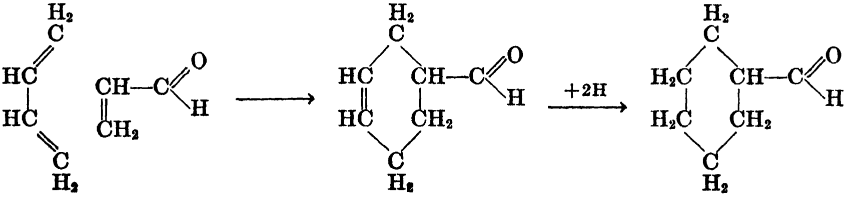
[67] Kuhn and Wagner-Jauregg, *Ber.*, 63, 2664 (1930). Alder and Stein, *Ann.*, 514, 197 (1934).

[68] Dupont and Germain, *Compt. rend.*, 223, 743 (1946); *Chem. Abstracts*, 41, 2420 (1947).

[69] Petrov, *Compt. rend. acad. sci. U.R.S.S.*, 53, 527 (1946); *C.A.*, 41, 3070 (1947).

In the following sections will be found examples which have been chosen to illustrate and expand the material so far presented.

(1) HYDROBENZALDEHYDES AND HYDROBENZOIC ACIDS. By heating equimolecular amounts of acrolein and butadiene in a pressure tube at 100°C. (preferably in the presence of a small amount of hydroquinone) 1,2,3,6-tetrahydrobenzaldehyde (LXIX) is formed. Catalytic reduction of the double bond results in the corresponding hexahydrobenzaldehyde (LXX).

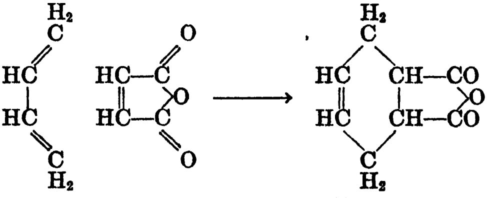


(LXIX) (LXX)

Application of this method[47,70–72] to homologues of butadiene often necessitates the use of high temperatures to insure reaction. Thus the corresponding acid is often used in place of the aldehyde to eliminate side reactions due to the very active aldehyde group.

The partially and completely hydrogenated homologues of benzaldehyde and benzoic acid, which are so obtained, were previously unattainable or could only be secured by indirect methods. The resulting aldehydes may be transformed by known methods into perfumes of the ionone type.

(2) PHTHALIC ACIDS AND THEIR HYDROGENATED DERIVATIVES. Butadiene and maleic anhydride, when allowed to react together in benzene solution at room temperature give a quantitative yield of *cis*-1,2,3,6-tetrahydrophthalic anhydride (LXXI). The oxidation of the adduct leads to butane-1,2,3,4-tetracarboxylic acid (LXXII), while catalytic reduction gives *cis*-hexahydrophthalic anhydride (LXXIII).[70,73,74]



(LXXI)

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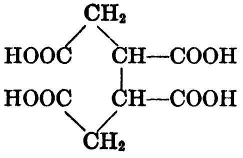
[70] Diels and Alder, *Ann.*, **460**, 98 (1928).

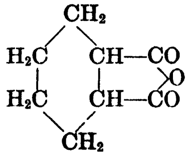
[71] Naef and Cie, French Patent, 672,025; *Chem. Zentr.*, **1930,I**, 2796; *Chem. Abstracts*, **24**, 2243 (1930).

[72] Schorygin and Guseva, *Chem. J., Series A, J. Gen. Chem.* (*U. S. S. R.*), **6**, (68), 1569 (1936); *Chem. Zentr.*, **1937,I**, 2038; *Chem. Abstracts*, **31**, 2184 (1937).

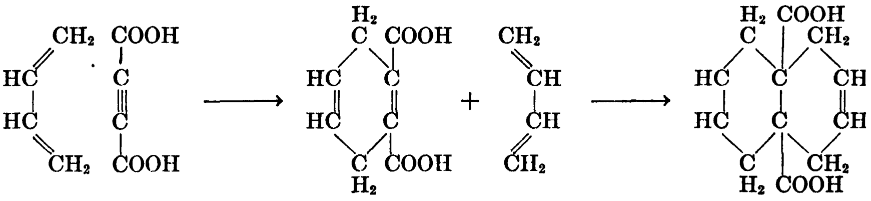
[73] Jenkins and Costello, *J. Am. Chem. Soc.*, **68**, 2733 (1946).

[74] Diels and Alder, *Ber.*, **62**, 2087 (1929).


(LXXII)


(LXXIII)

If acetylenedicarboxylic acid is substituted for maleic anhydride in the previously described diene synthesis, 3,6-dihydrophthalic acid (LXXIV) is obtained. Since this is a substituted maleic acid, it can enter into a second diene synthesis with butadiene to yield a dicarboxylic acid (LXXV) of the hexahydronaphthalene series.[75,76]


(LXXIV) (LXXV)

The adducts, LXXI and LXXIV, of butadiene with maleic and acetylenedicarboxylic acids, respectively, may be dehydrogenated by known methods (S or halogen) to phthalic acids. In these simple cases the dehydrogenation is of use only as a method of constitutional proof. It attains importance as a synthetic method, however, with the adducts of the homologues of butadiene. This new route to the phthalic acid series[77] is a valuable advance in preparative organic methods. Only a few of the products which may be obtained have been investigated with respect to their use in the synthesis of plastics (glyptals) and dyes (phthalein, phthalocyanine, and anthraquinone).

The esters of sorbic[78] and muconic acids[79] have proved valuable in the synthesis of derivatives of cyclohexenetri- and tetracarboxylic acids (LXXI and LXXVII). Hydrolysis yields the free acids.

Surprisingly enough the esters of ethylenetetracarboxylic acid (LXXVIII), which possess the highest possible degree of substitution, are very active dienophiles. For example, the ethyl ester allowed to react with butadiene at 170° yields ethyl-1,2,3,6-tetrahydrobenzene-1,1,2,2-

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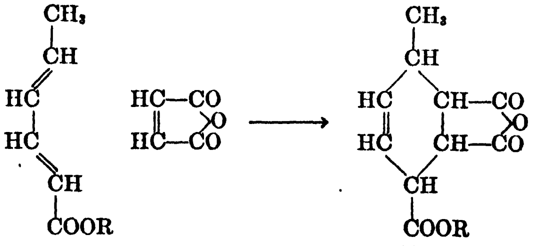
[75] Alder and Backendorf, *Ber.*, **71**, 2199 (1938).

[76] Brigl and Herrmann, *Ber.*, **71**, 2280 (1938).

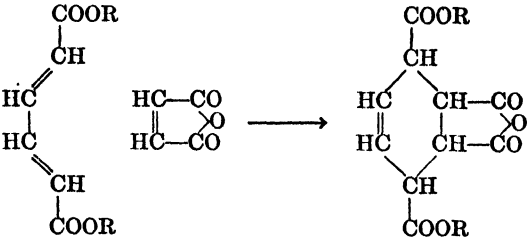
[77] Compare the series of reactions on pages 416 and 472.

[78] Wagner-Jauregg and Helmert, *Ber.*, **71**, 2535 (1938); older literature references here.

[79] Farmer and Warren, *J. Chem. Soc.*, **1929**, 904. I. G. Farbenindustrie A.-G., Swiss Patents, 143,242–143,257, inclusive; *Chem. Zentr.*, **1931,I**, 2938. Compare in regard to this Smith and Carlson, *J. Am. Chem. Soc.*, **61**, 288 (1939).

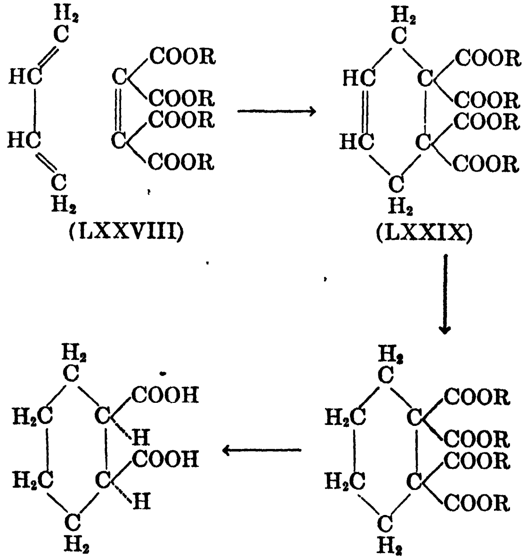


(LXXVI)



(LXXVII)

tetracarboxylate (LXXIX). This compound is converted into hexahydro-*o*-phthalic acid by hydrogenation, hydrolysis, and decarboxylation, a degradation which unequivocally establishes the addition as a diene synthesis.[65]



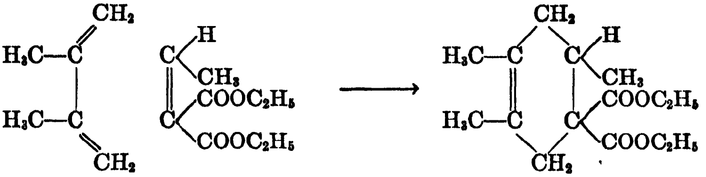
(LXXVIII)

(LXXIX)

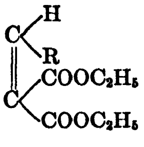
(3) ALICYCLIC MALONIC ESTERS AND ACETOACETIC ESTERS.[65,66] Methylenemalonic ester (LXXXII) (R = H, CH_3, C_2H_5, *i*-C_3H_7, C_6H_5)

and its homologues add dienes in a surprisingly smooth reaction to form alicyclic malonic esters.

The addition of 2,3-dimethylbutadiene to ethylidenemalonic ester (LXXX) yields the diethyl ester of 2,4,5-trimethylcyclohexene-1,1-dicarboxylic acid (LXXXI).

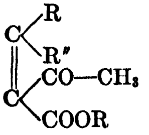


(LXXX) (LXXXI)

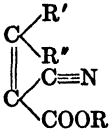


(LXXXII)

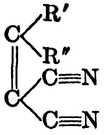
This type of addition is capable of many variations. In addition to the homologues and analogues of both components, alkylideneacetoacetic esters (LXXXIII), alkylidenecyanoacetic esters (LXXXIV), and alkylidene malonodinitriles (LXXXV) may be used as dienophiles and yield the expected products. The new alicyclic compounds can, in turn, form the starting materials for further synthesis.



(LXXXIII)



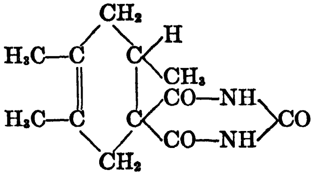
(LXXXIV)



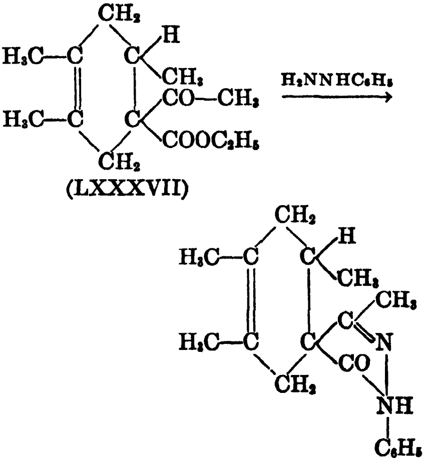
(LXXXV)

R′ = H; R″ = alkyl or aryl

The formation of heterocyclic combinations is especially important. For example, a barbituric acid derivative (LXXXVI) is obtained from the



(LXXXVI)



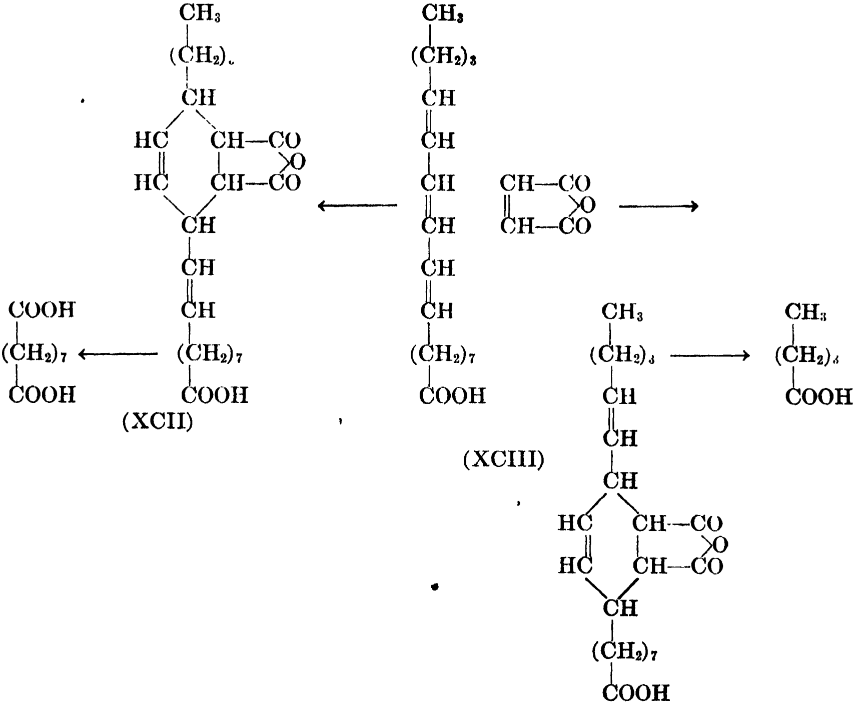
(LXXXVII)

(LXXXVIII)

ester LXXXI and urea. The adduct (LXXXVII) of 2,3-dimethylbutadiene and ethylideneacetoacetic ester reacts with phenylhydrazine to form a pyrazolone derivative (LXXXVIII).[65]

(4) DIENE SYNTHESES WITH HIGHER FATTY ACIDS. A special group of carboxylic acids can be obtained by making use of the fatty acids with multiple double bonds. The necessary condition of the reaction is conjugation of the double bonds in the fatty acid chain. This condition is satisfied in the dehydration product of ricinoleic acid,[80,81] the octadeca-9,11-dienoic acid (LXXXIX), and in the two naturally occurring fatty acids, eleostearic acid[81,82] (XC) from china wood oil and licanic acid[83] (XCI) from oiticica oil.

$$H_3C—(CH_2)_5—CH{=}CH—CH{=}CH—(CH_2)_7—COOH \qquad \text{(LXXXIX)}$$
$$H_3C—(CH_2)_3—CH{=}CH—CH{=}CH—CH{=}CH—(CH_2)_7—COOH \qquad \text{(XC)}$$
$$H_3C—(CH_2)_3—CH{=}CH—CH{=}CH—CH{=}CH—(CH_2)_4—CO—(CH_2)_2—COOH \qquad \text{(XCI)}$$


(XCII)

(XCIII)

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[80] Böeseken and Hövers, *Rec. trav. chim.*, 49, 1165 (1930).

[81] Kaufmann and Baltes, *Fette u. Seifen*, 43, 93 (1936).

[82] Morrel and Samuel, *J. Chem. Soc.*, 1932, 2251.

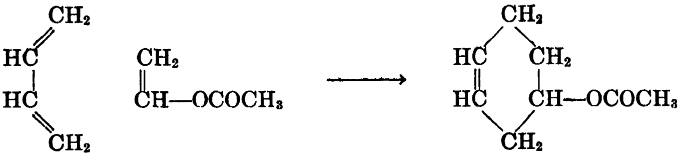
[83] Kaufmann and Baltes, *Ber.*, 69, 2679 (1936). Morrel and Davis, *J. Chem. Soc.*, 1936, 1481.

Eleostearic and licanic acids occur in two *cis-trans* isomeric forms.[84] Viewed from the standpoint of the diene synthesis it is interesting that all five acids add maleic anhydride with great ease at 100°C. in benzene solution. The addition is normal; *i.e.*, in every case a six-membered ring is formed.[84a] This also applies to the triene system. In this case, the spatial configuration at the double bonds determines at which end of the system the 1,4 addition occurs, as shown in the case of the stereoisomeric α- and β-eleostearic acids.

The α isomer gives 6-*n*-butyl-3-carboxynonenyl-1,2,3,6-tetrahydrophthalic anhydride (XCII) with maleic anhydride; the β form leads to 6-hexenyl-3-carboxyheptyl-1,2,3,6-tetrahydrophthalic anhydride (XCIII). The acid (XCII) yields azelaic acid and XCIII yields *n*-valeric acid by oxidative degradation. This same dependency of the course of the diene synthesis on the configuration of the unsaturated acid is encountered with the two stereoisomeric licanic acids.

The diene synthesis has acquired considerable importance in the chemistry of fats. It is used to estimate the conjugated double bonds in fatty acids (diene number, dienometry). It has contributed to the understanding of the drying process and of emulsion formation, as well as to the preparation and modification of lacquers.

Up to this point only dienophiles with the groupings C=C—C=O, C=C—C≡N, and C≡C—C=O have been discussed. Systematic studies have demonstrated that in place of C=O and C≡N an adjacent —C=C— linkage will activate the double bond. Indeed, in some cases the conjugation of the unsaturated linkages may be interrupted without destroying the ability of the double bond to undergo diene synthesis. This last type of addition is encountered in the addition of the esters of vinyl alcohol. For example, 3-cyclohexene-1-ol-acetate (XCIV) is obtained from vinyl acetate and butadiene at 180°C.[85]



(XCIV)

The yields obtained in the above reaction are usually small. This is attributed to the fact that such diene syntheses proceed very slowly.

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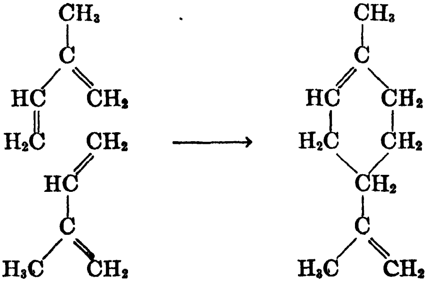
[84] Concerning a structural isomer of eleostearic acid and its diene synthesis with maleic anhydride see Kass and Burr, *J. Am. Chem. Soc.*, **61**, 3292 (1940).

[84a] *Cf.* Kurata and Miyoshi, *J. Chem. Soc. Japan*, **63**, 1151 (1942); *Chem. Abstracts*, **41**, 3755 (1947).

[85] Alder and Rickert, *Ann.*, **543**, 1 (1940).

Although the unused vinyl acetate can be recovered unchanged, the diene is lost by a concurrent dimerization.

These dimerization processes are of interest in the synthesis of compounds of the cyclohexene series. Dipentene formation from isoprene is the classical example of this kind. It demonstrates that the hydrocarbon may assume the double function of a diene and dienophile (partial 1,4 addition):



In so far as they have been investigated, the simple diene hydrocarbons and other hydrocarbons with conjugated double bonds dimerize according to this scheme.[86] Numerous cyclohexene derivatives can be obtained readily in this way, but quite often, subsequent reactions complicate the picture.[87]

The synthesis of hydrocarbons according to the scheme of partial 1,4 addition suggests that simple unsaturated hydrocarbons such as ethylene or propylene may assume the role of dienophiles. Additions of this type have been observed in some cases. For preparative purposes, especially when an unstirred liquid phase is used in the absence of a catalyst, the presence of a second double bond is usually necessary. However, under extreme conditions the above type of synthesis appears quite possible,[88] and many aromatic hydrocarbons which arise by pyrogenic processes owe their formation to it.

An aromatic nucleus adjacent to a double bond in a dienophile (styrene type) confers an activation similar to that of a double bond. This will be discussed in a following section.

B. Polynuclear Systems

(1) UNCONDENSED TYPES. This type of compound is obtained by

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[86] Compare this with the treatise of Alder (foot-note 1), "Die Methoden der Diensynthese," p. 3114 ff.; Wagner-Jauregg, *Ann.*, 488, 176 (1931). Of the more recent work may be mentioned the dimer of 2,3-dimethylbutadiene (Farmer and Martin, *J. Chem. Soc.*, 1940, 1169) and the previous communication, the dimer of methyl sorbate [Farmer and Morrison-Jones, *ibid.*, 1940, 1339; Kuhn and Deutsch, *Ber.*, 65, 43 (1932)].

[87] See for example, Alder and Rickert, *Ber.*, 71, 373 (1938).

[88] Compare for example, Alder and Rickert, *Ann.*, 543, 1 (1940); Joshel and Butz, *J. Am. Chem. Soc.*, 63, 3350 (1941).

diene syntheses when open chain dienes and dienophiles are substituted with cyclic substituents and none of the double bonds of these substituents enter into the reaction.

(*a*) *Di-, Ter-, and Quaterphenyl Series; Highly Arylated Compounds.* The arylated derivatives of butadiene have been investigated quite intensively. The principal members of this series are collected in the following table:

1-Phenylbutadiene[89,90]	$H_5C_6—CH{=}CH—CH{=}CH_2$
2-Phenylbutadiene[91]	$H_2C{=}C(C_6H_5)—CH{=}CH_2$
1,2-Diphenylbutadiene[92]	$H_5C_6—CH{=}C(C_6H_5)—CH{=}CH_2$
1,3-Diphenylbutadiene[93]	$H_5C_6—CH{=}CH—C(C_6H_5){=}CH_2$
1,4-Diphenylbutadiene[89,94-96]	$H_5C_6—CH{=}CH—CH{=}CH—C_6H_5$
2,3-Diphenylbutadiene[97]	$H_2C{=}C(C_6H_5)—C(C_6H_5){=}CH_2$
1,2,4-Triphenylbutadiene[92]	$H_5C_6CH{=}C(C_6H_5)—CH{=}CH—C_6H_5$
1,2,3,4-Tetraphenylbutadiene[98]	$H_5C_6CH{=}C(C_6H_5)—C(C_6H_5){=}CH—C_6H_5$

With respect to the scope of the diene synthesis in this series, it may be noted that only the last mentioned hydrocarbon is incapable of adding dienophiles. There are, however, indications that substitution of three adjacent carbon atoms with aromatic groups causes similar inhibitions. In all other cases, the addition proceeds with the usual ease and takes a normal course. As a general rule, it may be stated that the reaction velocity decreases with increasing substitution of the unsaturated centers which enter into the reaction. For example, 1,4-diphenyl-1,3-butadiene reacts quite smoothly with highly reactive dienophiles, such as maleic anhydride or *p*-quinone, while the addition fails with less reactive compounds such as phenyl vinyl ketone. It should be recalled that 1,4-diphenyl-1,3-butadiene, until now, has been employed only in its *trans-trans* configuration. The behavior of the two other stereoisomers of this hydrocarbon is not yet known with any degree of certainty.

2,3-Diphenyl-1,3-butadiene undergoes the diene synthesis quite smoothly. This is noteworthy because 2,3-di-*tert*-butyl-1,3-butadiene is entirely unreactive, as has been mentioned in Section I (page 382). The

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[89] Diels and Alder, *Ber.*, 62, 2081 (1929).

[90] Diels, Alder, and Stein, *Ber.*, 62, 2337 (1929).

[91] Backer and Strating, *Rec. trav. chim.*, 53, 525 (1934). Carothers, U. S. Patent, 2,072,867.

[92] Bergmann and Bergmann, *J. Am. Chem. Soc.*, 62, 1699 (1940).

[93] Unpublished.

[94] Kuhn and Wagner-Jauregg, *Ber.*, 63, 2662 (1930).

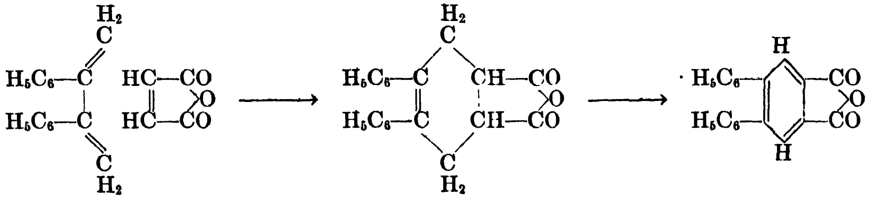
[95] Lohaus, *Ann.*, 516, 295 (1935). Weizmann *et al.*, *J. Chem. Soc.*, 1939, 391. Bergmann *et al.*, *J. Org. Chem.*, 7, 303 (1942).

[96] Bergmann and Schapiro, *J. Org. Chem.*, 12, 57 (1947).

[97] Alder and Rickert, unpublished. Allen *et al.*, *Can. J. Research*, 17B, 75 (1939).

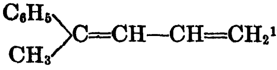
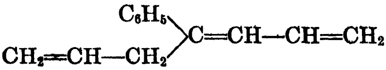
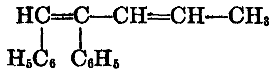
[98] Bergmann *et al.*, *Ann.*, 500, 122 (1933); *J. Chem. Soc.*, 1939, 391; *J. Am. Chem. Soc.*, 62, 1699 (1940).

addition of maleic anhydride to the former hydrocarbon has been selected to illustrate this entire group; 4,5-diphenyl-1,2,3,6-tetrahydrophthalic anhydride (XCV) may be synthesized in excellent yield according to the following scheme; it may be dehydrogenated by known methods to 4,5-diphenylphthalic anhydride (XCVI):


(XCV) (XCVI)

Arylated phthalic acids of this type possess considerable practical importance, as, for example, in the synthesis of octaphenylphthalocyanine dyes which were previously unknown.[99]

There are a number of examples in which the arylbutadienes possess additional substituents; thus compounds like:

1-Phenyl-4-methylbutadiene	$C_6H_5—CH{=}CH—CH{=}CH—CH_3$[89]
1-Phenyl-1-methylbutadiene	 $(C_6H_5)(CH_3)C{=}CH—CH{=}CH_2$[100]
1-Phenyl-1-allylbutadiene	 $(C_6H_5)(CH_2{=}CH—CH_2)C{=}CH—CH{=}CH_2$[100]
1,2-Diphenyl-4-methylbutadiene	 $HC(C_6H_5){=}C(C_6H_5)—CH{=}CH—CH_3$[92]
Cinnamylidene acetic ester	$H_5C_6—CH{=}CH—CH{=}CH—COOCH_3$[101]

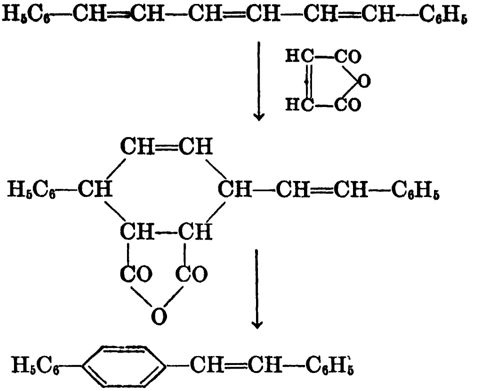
react normally and show sufficient tendency to add dienophiles so that they can be used in preparative work, at least if the respective dienophiles are rather reactive. As can be expected, the hydrogenation of the aromatic substituents does not change the additive properties of the diene system. Thus, 1-cyclohexyl-1,3-butadiene behaves like 1-phenyl-1,3-butadiene.

The ω,ω′-diphenylpolyenes form a distinctive group of arylated diene components. They show the expected behavior; *i.e.*, reaction occurs only through 1,4 addition.[94] Thus, the addition of maleic anhydride to 1,6-diphenyl-1,3,5-hexatriene (XCVII) gives the adduct (XCVIII) whose dehydrogenation and decarboxylation yields 1-phenyl-2-biphenylethylene (XCIX); 1,8-diphenyl-1,3,5,7-

[99] Alder, Hoyer, and Rickert, unpublished.

[100] Lehmann, *Ber.*, **68**, 1146 (1935); **69**, 631 (1936); **71**, 1869, 1874 (1938); **73**, 304 (1940).

[101] Allen and Overbaugh, *J. Am. Chem. Soc.*, **57**, 740 (1937).

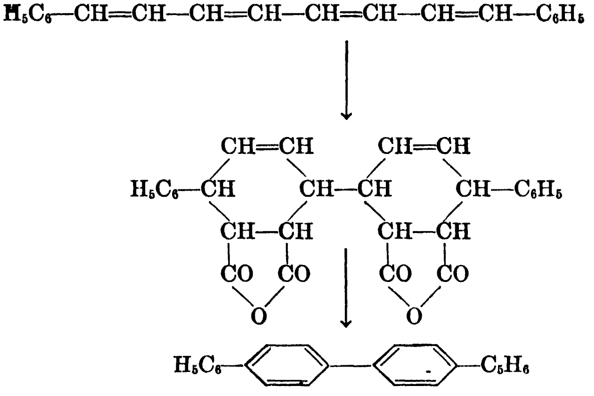


(XCVII)

(XCVIII)

(XCIX)

octatetraene (C) adds 2 moles of maleic anhydride. The reaction product (CI) may be degraded to quaterphenyl (CII).



(C)

(CI)

(CII)

We turn now to the dienophiles with cyclic substituents, especially those of an aromatic nature. First to be considered are compounds of the styrene type $C_6H_5CH{=}CH_2$,[102] such as cinnamaldehyde, $C_6H_5CH{=}CHCHO$,[103] cinnamic acid, $C_6H_5CH{=}CHCOOH$,[104] benzalacetone, $C_6H_5CH{=}CHCOCH_3$,[105] β-nitrostyrene, $C_6H_5CH{=}CHNO_2$,[106] and phenylpropiolic acid, $C_6H_5C{\equiv}CCOOH$.[107]

Styrene adds dienes in the usual manner but at high temperatures and in the presence of polymerization inhibitors. For example, the addition of 2,3-dimethylbutadiene leads to the formation of 3,4-dimethyl-1,2,5,6-tetrahydrobiphenyl (CIII).

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[102] Alder and Rickert, *Ber.*, **71**, 379 (1938).

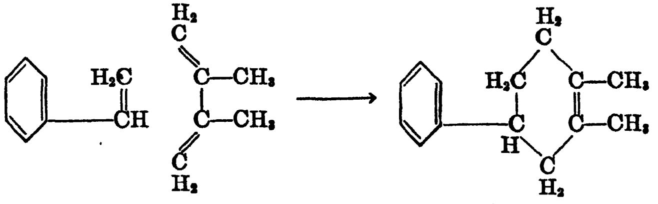
[103] Diels and Alder, *Ann.*, **470**, 62 (1929).

[104] I. G. Farbenindustrie A.-G., British Patent, 496,819; *Chem. Zentr.*, **1939**, **I**, 4396; *Chem. Abstracts*, **33**, 3603 (1939). Fuji *et al.*, *Ber.*, **69**, 2102 (1936).

[105] Unpublished observation.

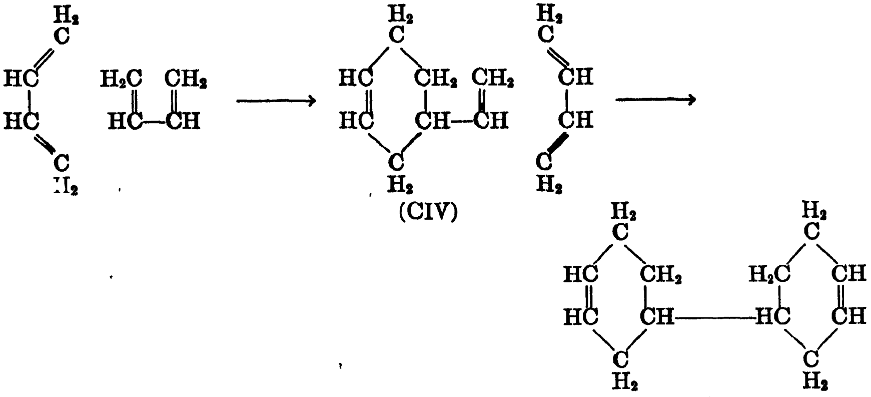
[106] Allen and Bell, *J. Am. Chem. Soc.*, **61**, 521 (1939). Sugasawa and Kodama, *Ber.*, **72**, 675 (1939).

[107] I. G. Farbenindustrie A.-G., and Dilthey, U. S. Patent, 2,097,854.



(CIII)

These additions may be varied in a great many ways and the yields are satisfactory for many preparative purposes. The tendency of styrene to add dienes is considerably decreased if the conjugation of the double bond with the benzene ring is destroyed. However, hydrocarbons of the vinyl-3-cyclohexene type (CIV) are still capable of the diene synthesis. For example, octahydro-3,3′-biphenyl (CV) is formed from butadiene and CIV.[87]



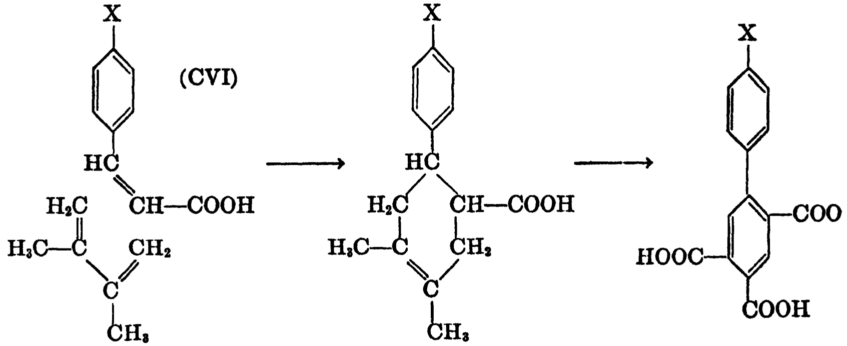
(CIV)

(CV)

Since the hydrocarbon (CIV) consists of 2 moles of butadiene, it is a dimer. Thus, compound CV represents the trimeric form of butadiene. This is one of the most convenient routes from the aliphatic into the biphenyl series.

Of all the dienophiles which have so far been considered, the α,β-unsaturated carbonyl compounds are the most important for preparative work. The cinnamic acid type has proved especially valuable for the synthesis of carboxylic acids of the biphenyl series. The synthesis of the tricarboxylic acids which have the general formula (CVIII) (X = H, Cl, OCH_3) may be mentioned as one of the most important results.

The addition of 2,3-dimethylbutadiene to cinnamic acids (CVI) yields the monocarboxylic acids (CVII) of the hydrogenated biphenyls. Dehydrogenation and subsequent oxidation of the two methyl groups give tricarboxylic acids (CVIII) of biphenyl.

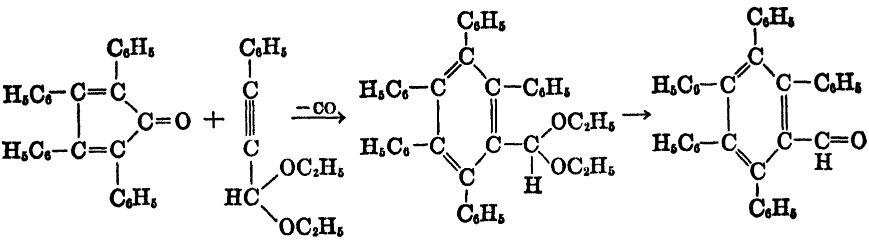


(CVI) (CVII) (CVIII)

The compounds of the type (CVIII) are substituted phthalic acids and as such have acquired significance in the synthesis of phthalocyanine dyes. The presence of carboxyl groups makes these dyes especially valuable because of the solubility which is conferred by this group.[108]

It scarcely need be mentioned that the arylated dienophiles may be combined with the arylated dienes. The results of such a union are a special massing of aromatic nuclei which have an arrangement similar to that of biphenyl.

Another variation of the diene synthesis in which cyclic dienes are employed as the starting materials leads to such highly arylated compounds in an especially elegant way. They will be more thoroughly discussed in the section on cyclic dienes. However, the synthesis of tetraphenylbenzaldehyde (CXII)[109] is mentioned here as a typical example. Tetraphenylcyclopentadienone (CIX) reacts with the diethyl acetal of phenylpropio-



(CIX) (CX) (CXI) (CXII)

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[108] I. G. Farbenindustrie A.-G., British Patent, 496,819; *Chem. Zentr.*, 1939,I, 4396; *Chem. Abstracts*, 33, 3603 (1939).

[109] Dilthey, I. G. Farbenindustrie A.-G., British Patent, 435,708; *Chem. Abstracts*, 30, 1388 (1936); Italian Patent, 319,169; *Chem. Zentr.*, 1936,I, 2838.

licaldehyde (CX) to yield an intermediate product, which immediately loses carbon monoxide, forming pentaphenylbenzaldehyde diethyl acetal (CXI), hydrolysis of which yields the free aldehyde (CXII).

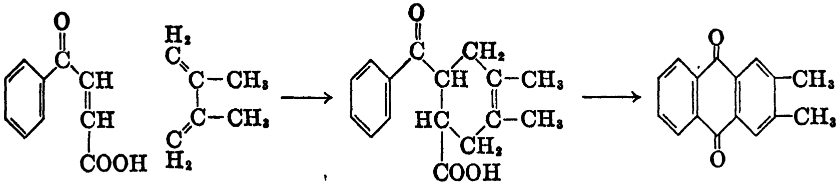
By a suitable choice of components the principle of the elimination of carbon monoxide during a diene synthesis can be utilized to yield a large variety of products. This variation is dealt with in detail on pages 457–63 and gives a picture of the flexibility of the method and its significance in the chemistry of polynuclear compounds.

(*b*) *Diphenylmethane Series.* Compounds of the diphenylmethane series may also be obtained by means of the diene synthesis, *i.e.*, by the use of such compounds as:

Vinyl phenyl ketone	$H_5C_6—CO—CH{=}CH_2$
Ethylideneacetophenone	$H_5C_6—CO—CH{=}CH—CH_3$
Benzalacetophenone	$H_5C_6—CH{=}CH—CO—C_6H_5$
Dibenzalacetone	$C_6H_5—CH{=}CH—CO—CH{=}CH—C_6H_5$
Dibenzoylethylene	$H_5C_6—CO—CH{=}CH—CO—C_6H_5$
Aroylacrylic acids	$Ar—CO—CH{=}CH—COOH$
Dibenzoylacetylene	$C_6H_5—CO—C{\equiv}C—CO—C_6H_5$

and similar types as dienophile components.[110,111]

The aroylacrylic acids (CXIII), which are obtained quite easily by the Friedel-Crafts reaction from maleic anhydride and aromatic hydrocarbons, combine with simple dienes at 100°C. in alcoholic solution in almost quantitative yields.[112]


(CXIII) (CXIV)

Subsequent ring closure and aromatization of the newly formed rings transforms the adducts into anthraquinone derivatives (CXIV).

The following example illustrates the many varieties of compounds which may be synthesized when dibenzoylethylene (CXV) is used as a dienophile. Thus, 1,2-dimethyl-4,5-dibenzoylcyclohexene (CXVI) is formed from 2,3-dimethylbutadiene and dibenzoylethylene. Since it is a 1,4-diketone, it may be transformed into the furan derivative (CXVII).

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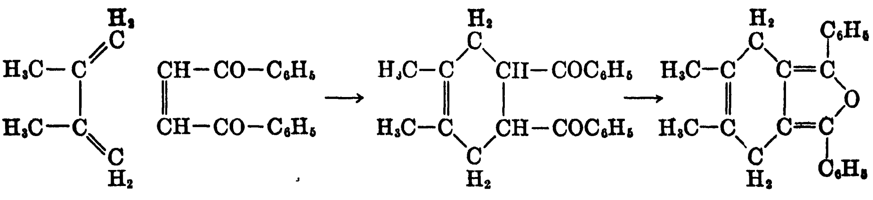
[110] I. G. Farbenindustrie A.-G. and Scheyer, German Patent, 597,325. Adams *et al.*, *J. Am. Chem. Soc.*, 62, 56, 1233 (1940). Dupont and Paquot, *Compt. rend.*, 205, 805 (1937).

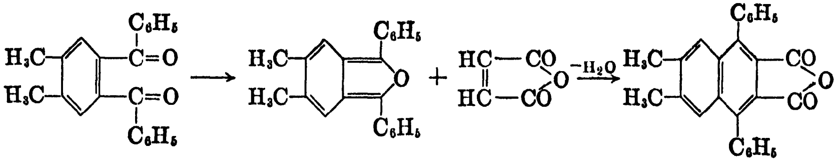
[111] Allen, *et al.*, *J. Am. Chem. Soc.*, 62, 656 (1940).

[112] Fieser and Fieser, *J. Am. Chem. Soc.*, 57, 1679 (1935).



(CXV) (CXVI) (CXVII)

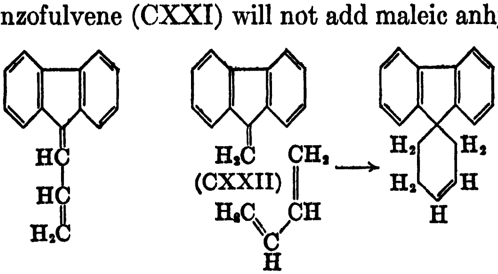
Hydrolysis and dehydrogenation of CXVII lead to 1,2-dimethyl-4,5-dibenzoylbenzene (CXVIII), which is transformed by reduction into dimethyl-α,α'-diphenyl-β,β'-benzofuran (CXIX). This new compound can again function as a diene and its use as such offers a convenient route to the naphthalene series. For example, with maleic anhydride the anhydride of 1,4-diphenyl-6,7-dimethylnaphthalene-2,3-dicarboxylic acid (CXX) is obtained.



(CXVIII) (CXIX) (CXX)

The chemistry of this type of diene synthesis is considered in detail on page 493 ff.

(2) Spirocyclic Types. Spirocyclic ring systems are formed in the diene synthesis when at least one of the double bonds which participate in the addition is semicyclic. The experimental data concerning this series are very meager. However, it appears from available evidence that semicyclic dienophiles are capable of adding to dienes. In contrast to this, dienes with a semicyclic double bond show no tendency to react in the diene synthesis. Thus biphenyleneethylene (CXXII) adds butadiene,[113] while vinyldibenzofulvene (CXXI) will not add maleic anhydride.[114]



(CXXII)

(CXXI)

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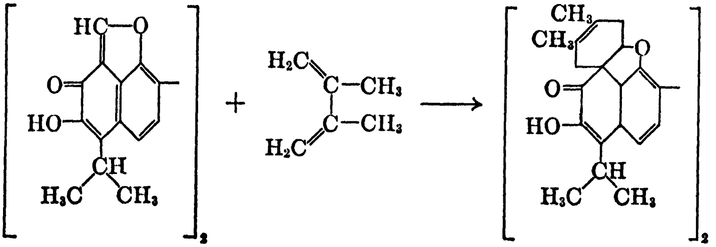
[113] Wieland and Probst, *Ann.*, **530**, 276 (1937).

[114] Backer and Strating, *Rec. trav. chim.*, **60**, 391 (1941).

The addition of simple dienhydrocarbons to anhydrogossypol appears to belong to the type of diene synthesis in which the dienophile is semicyclic.[115] For instance the addition of 2,3-dimethylbutadiene to anhydrogossypol is shown in the accompanying formulas.



This example illustrates the value of the diene synthesis as a method of determining structure, and the type of complex compounds which may be obtained in a relatively simple manner.

The formation of the spirocyclic configuration by means of the diene synthesis has been observed repeatedly in the heterocyclic series (see page 502).

(3) Condensed Types. Condensed ring systems can be formed when at least one of the three unsaturated linkages, which participate in the addition, is contained in a ring. This condition may be fulfilled by the diene or the dienophile component. The ring can possess either cycloaliphatic or aromatic character. As will be shown in the following, all possibilities have been realized.

(*a*) *Indene and Fluorene Series.* There have been comparatively few instances of a diene synthesis which lead directly to this type of ring.

The tendency of cyclic α,β-unsaturated ketones to add is relatively small. It may be increased if a second keto group is introduced adjacent to the first[116] (for instance by oxidation with SeO_2). Thus 1-methyl-1-cyclopentea-5-one (CXXIII) and 2,3-dimethylbutadiene yield a bicyclic ketone (CXXIV)[117] and 1-methyl-1-cyclopentene-4,5-dione (CXXV) is transformed by heating with butadiene into the diketone (CXXVI).

The angular position of the methyl group is characteristic of both adducts, CXXIV and CXXVI. It is common to both the five- and six-membered rings. Such arrangements occur in the steroids. It will be shown later that such additions yield various derivatives of the steroid system when carried out with complicated dienes.

A second route into the indene series starts with diacetylethylene and

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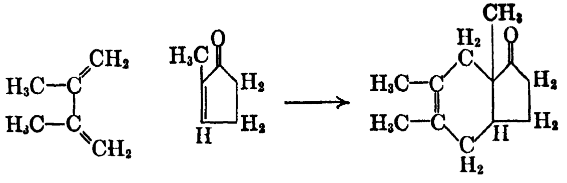
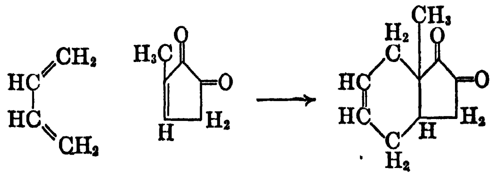
[115] Adams *et al.*, *J. Am. Chem. Soc.*, 60, 2193 (1938).
[116] Dane *et al.*, *Ann.*, 532, 29 (1937).
[117] Bockemüller, *Angew. Chem.*, 51, 188 (1938).

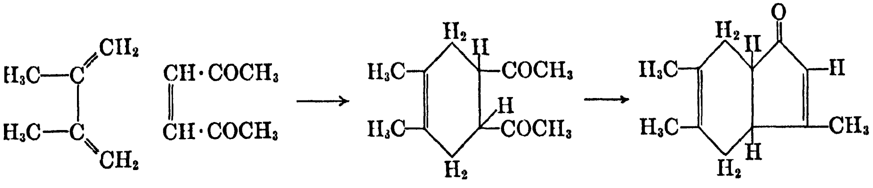


(CXXIII) (CXXIV)



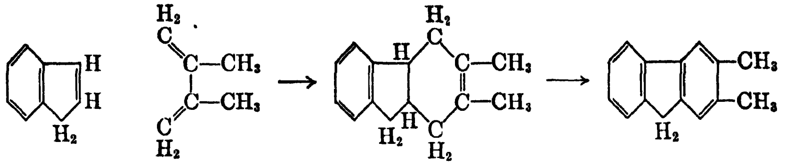
(CXXV) (CXXVI)

its homologues. For example, 2,3-dimethylbutadiene adds to diacetylethylene and the adduct (CXXVII) is transformed by subsequent intramolecular condensation into the indene type (CXXVIII).[118] This method is also applicable to the synthesis of the steroids.[119]



(CXXVII) (CXXVIII)

The ring system of fluorene results when compounds of the indene type function as dienophiles. Thus, a partially hydrogenated 2,3-dimethylfluorene (CXXIX) is formed when 2,3-dimethylbutadiene is heated with indene. This may be smoothly dehydrogenated to 2,3-dimethylfluorene (CXXX).[120]



(CXXIX) (CXXX)

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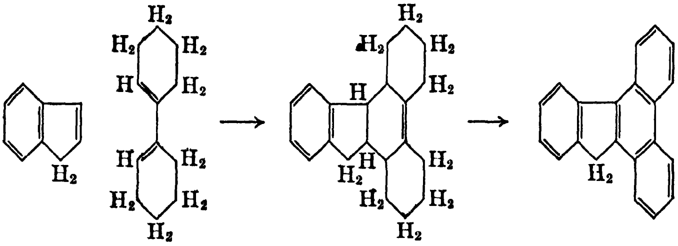
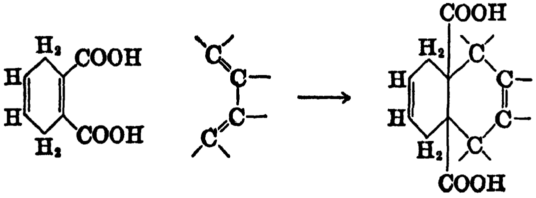
[118] Goldberg and Müller, *Helv. Chim. Acta*, 21, 1699 (1938).
[119] Goldberg and Müller, *Helv. Chim. Acta*, 23, 831 (1940).
[120] Alder and Rickert, *Ber.*, 71, 879 (1938).

A partially hydrogenated 1,2,3,4-dibenzofluorene (CXXXII) is formed in a similar manner when 1,1′-dicyclohexenyl (CXXXI) is used in place of butadiene. CXXXII is converted by dehydrogenation into the parent aromatic substance (CXXXIII).[121]



(CXXXI) (CXXXII) (CXXXIII)

(*b*) *Naphthalene Series.* The preparation of compounds of the naphthalene type by means of the diene synthesis has been realized in a great number of ways. The synthesis of partially hydrogenated naphthalenes from cyclic maleic acid derivatives of the 3,6-dihydrophthalic acid type has been considered briefly (page 409). The dicarboxylic acids obtained by this procedure are distinguished by the angular position of their carboxyl groups.[75,76]



Dienes, in which the double bond system is shared by the ring and the side chain, provide a second method of obtaining compounds with two fused six-membered rings. For example, the anhydride of an octalindicarboxylic acid (CXXXV) which has an angular methyl group[122] is obtained by the addition of maleic anhydride to 1-methyl-2-vinyl-1-cyclohexene (CXXXIV).

This procedure is very valuable as a synthetic method because of the comparatively easy preparation of the starting material[123] and the numer-

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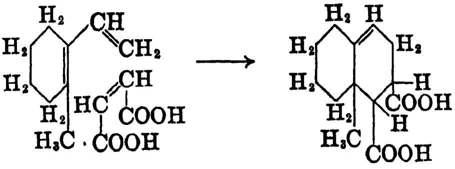
[121] Bergmann and Bergmann, *J. Am. Chem. Soc.*, 60, 1805 (1938). Bergmann and Weizmann, *J. Org. Chem.*, 9, 352 (1944).

[122] Meggy and Robinson, *Nature*, 140, 282 (1937). See also *J. Soc. Chem. Ind.*, 56, 512 (1937). For other additions of the same diene type see Cook and Lawrence, *J. Chem. Soc.*, 1938, 58; Dimroth, *Ber.*, 71, 1336 (1938); Backer and Strating, *Rec. trav. chim.*, 60, 391 (1941).

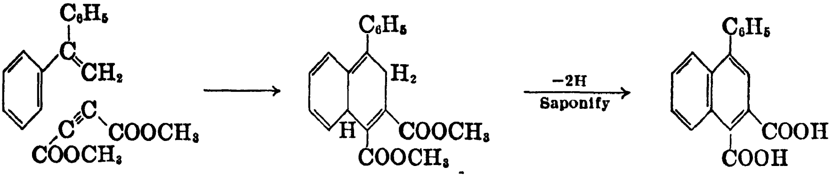
[123] From cyclic ketones and acetylene.



(CXXXIV) (CXXXV)

ous variations which may be employed. It is in no way confined to six-membered rings and has been used quite frequently and with excellent results for the preparation of polynuclear ring systems (see the following section).

A third route to the naphthalene series, similar to the method just described, but differing in several essential features, starts with dienes in which one of the two conjugated double bonds belongs to an aromatic nucleus. In this case, 1,4 addition occurs also. The aromatic character of the nucleus which is involved is partially destroyed, but is very easily restored by subsequent rearrangement and dehydrogenation of the adduct. For example, the addition of methyl acetylenedicarboxylate to *as*-diphenylethylene leads to 1-phenylnaphthalenedicarboxylic acid (CXXXVII).[124] The intermediate product (CXXXVI) is not isolated.



(CXXXVI) (CXXXVII)

If maleic anhydride is used a bis adduct is formed which can be converted to 1-phenyl-1,2,3,4-tetrahydronaphthalene-3,4-dicarboxylic acid by hydrogen iodide in acetic acid. Zinc dust distillation of this latter compound gives 1-phenylnaphthalene.[124] This reaction which has come to be known as the Wagner-Jauregg reaction has been investigated by Bergmann and co-workers. He has applied it to a number of 1,1-diarylethylenes and has found a convenient method for conversion of the bis adduct (A) into 1,6-disubstituted naphthalenes. Moreover when the two aryls are different the reaction follows the course predicted by the theory of resonance, *i.e.*, the ring with larger resonance contribution participates exclusively in the addition to the dienophile.[125]

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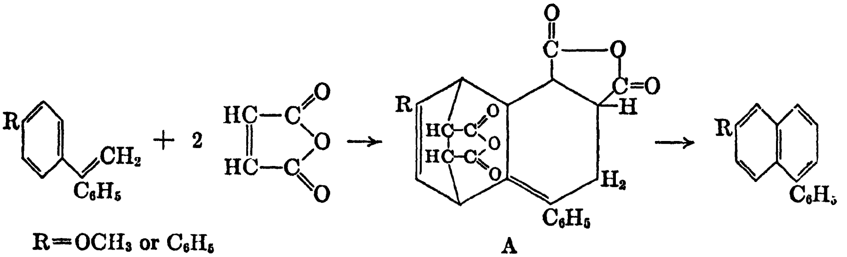
[124] Alder, Pascher, and Vagt, *Ber.*, 75B, 1501 (1942). Compare with this the addition of maleic anhydride with asymmetric diphenylethylene by Wagner-Jauregg, *Ann.*, 491, 1 (1931).

[125] Bergmann, Szmuszkowicz, and Fawaz, *J. Am. Chem. Soc.*, 69, 1773 (1947).



If diarylvinyl bromides are used in place of 1,1-diarylethylenes in the Wagner-Jauregg reaction the adducts upon sublimation in vacuum lose a mole of maleic anhydride, hydrogen bromide, and hydrogen with conversion to the fully aromatized naphthalene 1,2-anhydride.[126]

In contrast to the above, 1-phenyl-1-(α-naphthyl)-ethylene reacts with maleic anhydride to give a bis adduct that has been shown to be a derivative of 1,1-binaphthyl. This unexpected participation of the phenyl rather than the naphthyl group is attributed to the ortho effect. An *o*-methyl substituent in one of the phenyl groups of 1,1-diphenylethylene orients an addition involving the unsubstituted phenyl group. An ortho methoxy group in either or both of the aryl groups blocks the addition of maleic anhydride. Diarylethylenes containing the β-naphthyl or 9-phenanthryl groups give low yields of adducts of unestablished structure.[127]

Methylation of the side chain of vinylnaphthalenes reduces the activity to such a degree that a Diels-Alder reaction does not constitute a practical method for the synthesis of alkylated phenanthrenes.[128]

These procedures, which depend on the reactivity of styrene type compounds toward dienes, are capable of many modifications. The applicability is often limited with styrene and its simple homologues by the strong tendency of these compounds to polymerize either with themselves or with the dienophile.[129] The more complex compounds of this series which have an olefinic double bond incorporated in an alicyclic ring show very little, if any, tendency for homo- or heteropolymerization. There are many suitable diene components of this type, which may be used in the synthesis of fused ring systems. Other aromatic hydrocarbon radicals may be used in place of the phenyl nucleus. Thus 1- and 2-vinylnaphthalene (CXXXVIII and CXXXIX), 1- and 2-cyclopentenylnaphthalene (CXL and CXLI), and 9-cyclopentenylphenanthrene (CXLII) are a few of the many compounds with aromatic-aliphatic conjugation which may be used in the diene synthesis. The resulting compounds belong, respectively, to the phenanthrene, cyclopentenophenanthrene, and cyclopentenotriphenylene class.[92,130,131]

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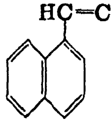
[126] Bergmann and Szmuszkowicz, *J. Am. Chem. Soc.*, 69, 1777 (1947).

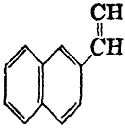
[127] Szmuszkowicz and Bergmann, *J. Am. Chem. Soc.*, 69, 1779 (1947).

[128] Bergmann and Weizmann, *J. Org. Chem.*, 11, 592 (1946).

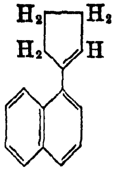
[129] See for example the addition of maleic anhydride to styrene, which leads to high molecular mixed polymerization, [Wagner-Jauregg, *Ber.*, 63, 3213 (1930)].



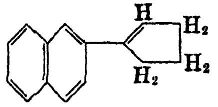
(CXXXVIII)



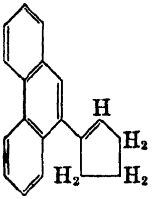
(CXXXIX)



(CXL)



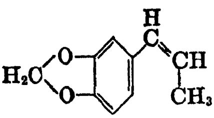
(CXLI)



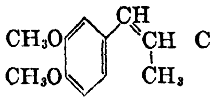
(CXLII)

The hydrocarbons necessary for this type of synthesis may be obtained by a method which is quite general and capable of considerable variation; aromatic Grignard reagents are added to carbonyl groups and water is split out from the resulting carbinols.

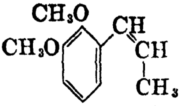
This method has been further extended in the styrene series. The accompanying compounds have a semicyclic diene system in which one double bond is part of an aromatic ring. These compounds add maleic anhydride, ethyl maleate, ethyl acetylenedicarboxylate, and chloromaleic anhydride to give naphthalene derivatives. Hudson and Robinson state that naphthalene derivatives are formed only when (*1*) there is a meta-alkoxy group, which is of course para to the carbon atom of the benzene



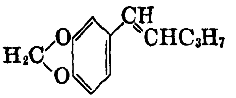
Isosafrole



Isoeugenol methyl ether



2,3-Dimethoxypropenylbenzene



Methylenedioxy-β-propylstyrene

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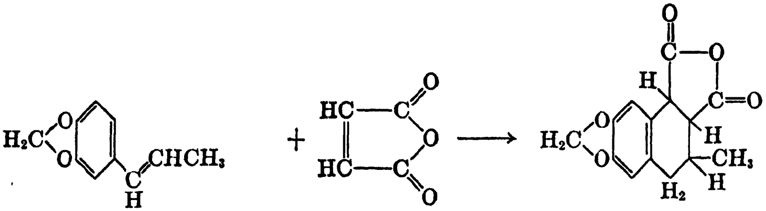
[130] Cohen and Warren, *Nature*, 136, 869 (1935); *J. Chem. Soc.*, 1937, 1315. Bergmann *et al.*, *J. Am. Chem. Soc.*, 59, 1443 (1937); 60, 1331, 1805 (1938). The latter claims anethol and styrene likewise add maleic anhydride (see page 425).

[131] Bachmann and Kloetzel, *J. Am. Chem. Soc.*, 60, 2204 (1938).

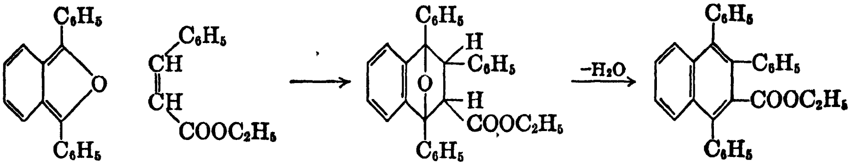
ring involved in the cyclization and (*2*) the styrene derivative is β-alkylated.[132]



(CXLIII) (CXLIV)

The tetrahydro compound (CXLIV) arising from the addition of maleic anhydride to isosafrole (CXLIII) may be smoothly dehydrogenated to the corresponding aromatic compound.

Another variation of the diene synthesis which has often been used with considerable success in the synthesis of naphthalene derivatives consists in the use of a heterocyclic diene of the furan type as a starting material. The adduct, which is formed in the normal manner, is easily converted into an aromatic derivative. This reaction will be considered in more detail in a subsequent section (see p. 493 ff.). The synthesis of ethyl 1,2,4-triphenylnaphthalene-3-carboxylate (CXLVII) will be cited here as an example of its use.[133] α,α′-Diphenyl-β,β′-benzofuran (CXLV) and cinnamic acid serve as the generators. The union of these components results in the adduct (CXLVI) which is easily converted by the elimination of water into the naphthalene derivative (CXLVII). The reaction may be carried out in one operation and gives the product in a yield of 80%.



(CXLV) (CXLVI) (CXLVII)

A great number of arylated compounds of the naphthalene, anthracene, and naphthacene series (*cf.* the following section), have been prepared recently in this way.

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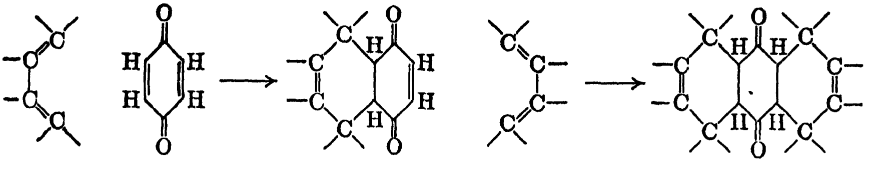
[132] Hudson and Robinson, *J. Chem. Soc.*, **1941**, 715. Bruckner, *Ber.*, **75**, 2034 (1942). Synerholm, *J. Am. Chem. Soc.*, **67**, 1229 (1945). *Cf.* Tomayo *et al.*, *An. fis. quim.*, **37**, 392, 397 (1941); *Chem. Abstracts*, **37**, 1707 (1943). *An. fis. quim.*, **38**, 184 (1942); *Chem. Abstracts*, **37**, 5034 (1943). *An. fis. quim.*, **39**, 209 (1943); *Chem. Abstracts*, **38**, 1214 (1944).

[133] Weiss and Beller, *Monatsh.*, **61**, 143 (1932).

The conversion of this type of compound into the naphthalene derivatives is illustrated by one of the first known examples, the addition of dienes to *p*-benzoquinone and its derivatives.

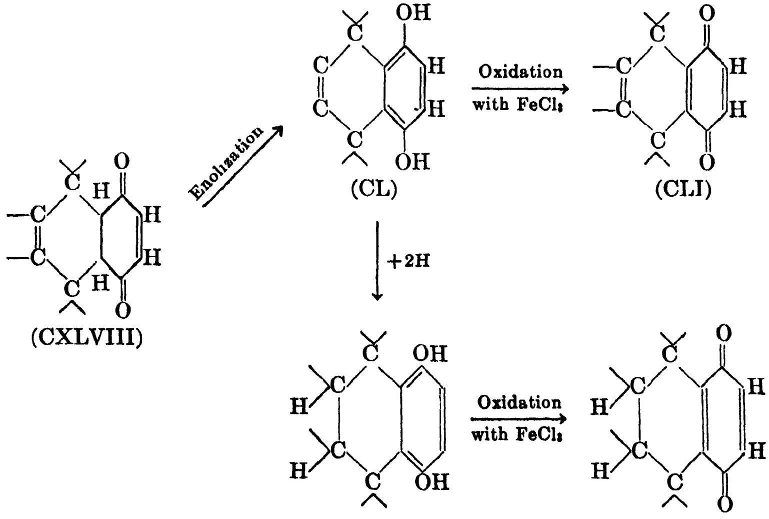
Depending on the quantity used and the conditions of the reaction, *p*-benzoquinone may add 1 or 2 moles of a diene and thereby yield a tetrahydronaphtho- (CXLVIII) or an octahydroanthraquinone derivative (CXLIX).



(CXLVIII) (CXLIX)

An interesting case of this type is the addition of butadiene to 2-methylbenzoquinone to give 2-methyltetrahydronaphthoquinone which can be dehydrogenated by heat to 2-methylnaphthoquinone, a substance which has been studied extensively in connection with work on vitamin K.[134]

The preparation of "monodienequinones" (CXLVIII) is of considerable value in that this previously unknown type of hydrogenated α-naphthoquinone is capable of further transformations. These lead to a new



(CL) (CLI) (CXLVIII) (CLII) (CLIII)

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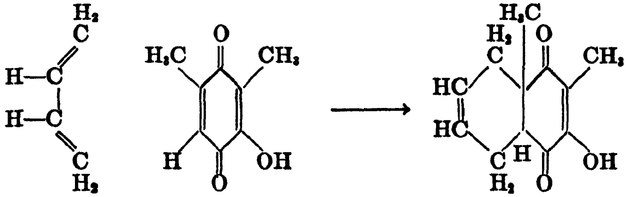
[134] Okahara and Murata, *J. Chem. Soc. Japan*, 63, 1354 (1942); *Chem. Abstracts*, 41, 3088 (1947).

class of compounds and make available compounds which were previously difficult to prepare.[51,135] The smooth isomerization of monodienequinones to 1,4-dihydro-α-naphthohydroquinones (CL) may be cited as an example of the versatility of these compounds. This isomerization (enolization) occurs easily by virtue of the angular position of the hydrogen atoms. Further examples are the preparation of 1,4-dihydro-α-naphthoquinone (CLI), which is obtained by careful oxidation of CL, and finally the formation of 1,2,3,4-tetrahydronaphthohydroquinone (CLII) and of 1,2,3,4-tetrahydro-α-naphthoquinone (CLIII) from CL.

The synthesis of hydrogenated α-naphthoquinones and hydroxy-α-naphthoquinones with angular substituents (R = CH_3, Cl) has been accomplished by the use of substituted *p*-benzoquinones (*p*-xyloquinones, thymoquinones, and chloranil).[136–138] The addition of butadiene to hydroxyxyloquinone (CLIV) takes place almost quantitatively by heating the components for 20 hours at 110° in dioxane solution.[70,139] Other dienes may be employed in these syntheses.



(CLIV)

(*c*) *Anthracene and Naphthacene Series.* The synthesis of compounds of this series depends to a large extent on the methods which have just been illustrated for the synthesis of naphthalene derivatives. The following description will be limited to those properties which are characteristic of this series. The methods in which quinones are employed as starting materials are among the most useful. Compounds of the anthracene system are synthesized either through the addition of 2 moles of diene to 1 mole of benzoquinone (bisdienequinone) (CLV) or by the addition of 1 mole of diene to 1 mole of α-naphthoquinone (CLVII)[140]:

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[135] Alder and Stein, *Ber.*, 62, 2345 (1929); *Ann.*, 501, 250 (1933). I. G. Farbenindustrie A.-G., British Patent, 324,661; *Chem. Zentr.*, 1939,II, 809; *Chem. Abstracts*, 24, 3801 (1930); Diels and Alder, German Patent, 521,621; *Chem. Zentr.*, 1931,II, 1758; *Chem. Abstracts*, 25, 3363 (1931). Bergmann and Bergmann, *J. Org. Chem.*, 3, 125 (1938). Fieser *et al.*, *J. Am. Chem. Soc.*, 61, 2206 (1939); 62, 2861, 2866 (1940).

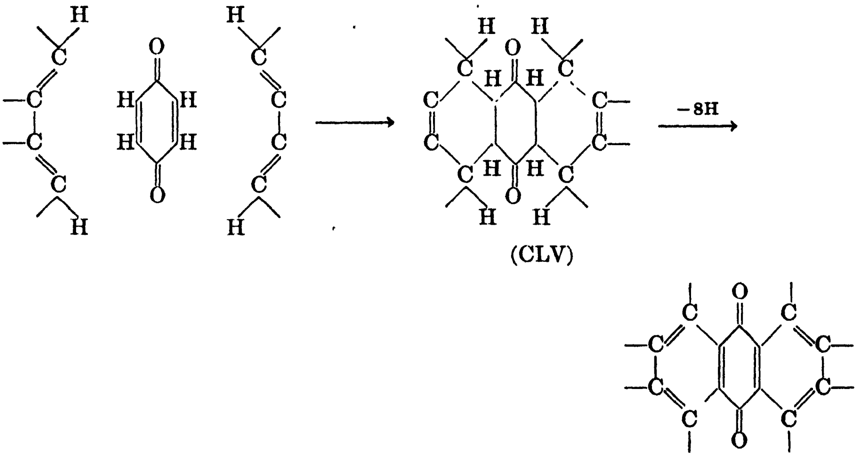
[136] Alder, *Arkiv Kemi, Mineral. Geol.*, B, 11, No. 49, 1 (1935). Fieser and Seligmann, *J. Am. Chem. Soc.*, 56, 2690 (1934); *Ber.*, 68, 1747 (1935).

[137] Posternak, *Helv. Chim. Acta*, 21, 1326 (1938).

[138] Fieser and Bradsher, *J. Am. Chem. Soc.*, 61, 417 (1939).

[139] Alder and Stein, *Ber.*, 62, 2337 (1929); *Ann.*, 501, 247 (1933).

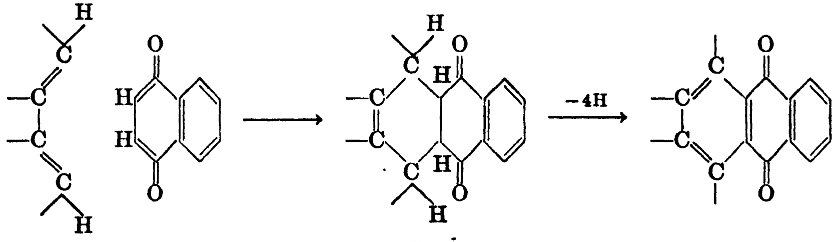
[140] Dane and Schmitt, *Ann.*, 536, 202 (1938).



(CLV)

(CLVI)

In the first instance an octahydroanthraquinone of the type (CLV) with 4 angular hydrogen atoms or substituents[141] is formed and in the



(CLVII)

(CLVIII)

second a tetrahydroanthraquinone (CLVII) with 2 angular hydrogen atoms is the product. The most important reaction[142] which these classes of compounds undergo is a remarkably smooth dehydrogenation to the parent substances (CLVI and CLVIII). In the first case 8 hydrogen atoms are eliminated and in the second, 4. For example, treatment of the adducts, CLV and CLVII, with air in alkaline media or merely heating in a mild oxidizing solvent like nitrobenzene will accomplish this dehydrogenation. The wide scope of this reaction and the great reactivity of these compounds have attracted many workers to this field. Consequently the chemistry of anthraquinone has been considerably enriched and expanded by the diene synthesis.[143,144]

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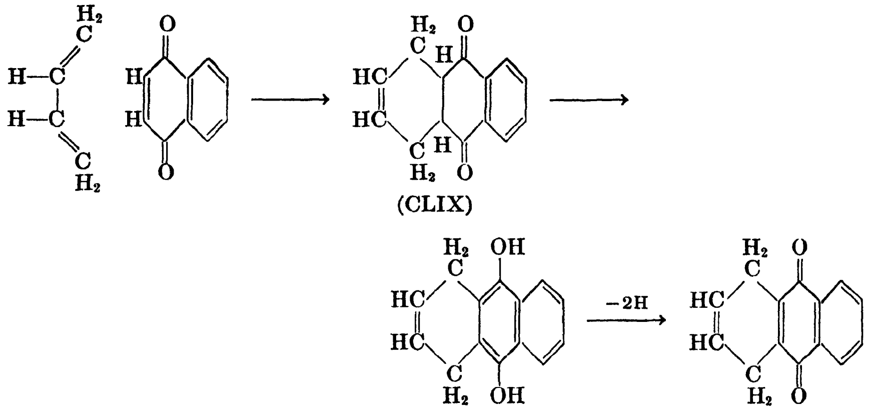
[141] The numerous experiments which have for their goal the synthesis of hydrogenated anthraquinones with angular substituents can merely be mentioned in this article; compare for example Fieser and Seligmann, *J. Am. Chem. Soc.*, **56**, 2690 (1934); *Ber.*, **68**, 1747 (1935).

[142] For their interesting steric rearrangements, which disclose considerable information regarding the ring arrangement compare Alder and Stein, *Ann.*, **501**, 247 (1933).

The dehydrogenation of the tetrahydroanthraquinone type (CLVII) which is easily obtained from α-naphthoquinone and a diene may be conducted in such a way (*i.e.*, by reaction under very mild conditions) that only the 2 angular hydrogen atoms are eliminated. A previously unknown 1,4-dihydroanthraquinone is thus formed. For example, the addition of butadiene to α-naphthoquinone gives the anthraquinone (CLIX) which is converted to 1,4-dihydroanthrahydroquinone (CLX) by treatment with palladium. This compound loses 2 hydrogen atoms by aerial oxidation during crystallization and is transformed into 1,4-dihydroanthraquinone (CLXI).



(CLIX)

(CLX) (CLXI)

If 1,1-disubstituted derivatives of butadiene are allowed to react with a naphthoquinone in this type of synthesis, then the final product may be obtained by the energetic dehydrogenation of the intermediate tetrahydroanthraquinone. Thus 1,1,3-trimethylbutadiene and α-naphthoquinone yield an adduct (CLXII) which can be dehydrogenated with air in al-

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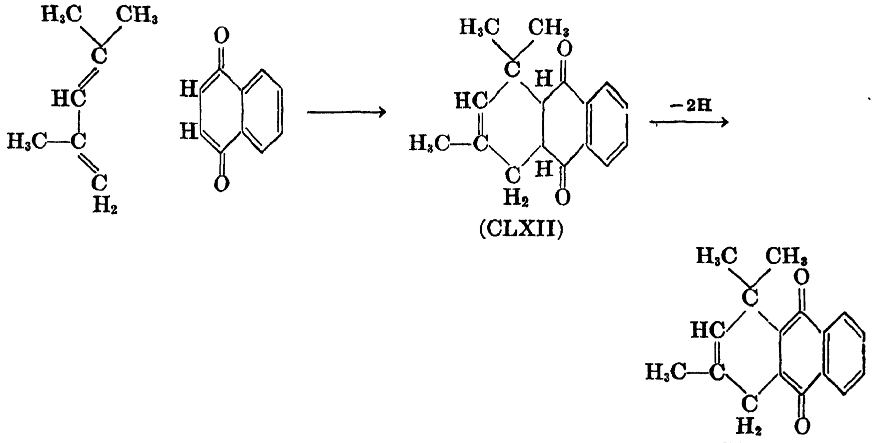
[143] Besides the work outlined above may be mentioned I. G. Farbenindustrie A.-G., German Patent, 494,433; *Chem. Abstracts*, **24**, 2757 (1930); French Patent, 673,825; *Chem. Abstracts*, **24**, 2757 (1930); Luttringhaus *et al.*, German Patent, 496,393; *Chem. Abstracts*, **24**, 3249 (1930); I. G. Farbenindustrie A.-G., British Patents, 320,375; *Chem. Abstracts*, **24**, 2757 (1930); 327,128; *Chem. Abstracts*, **24**, 5045 (1930), (*Chem. Zentr.*, **1930,II**, 807 ff.); Carothers *et al.*, *J. Am. Chem. Soc.*, **53**, 4204 (1931); **54**, 4071 (1932); **55**, 786, 1624, 2813, (1933); Fieser *et al.*, *ibid.*, **62**, 153, 1360 (1940); Weizmann, Bergmann, and Berlin, *ibid.*, **60**, 1331 (1938); Weizmann, Bergmann, and Haskelberg, *J. Chem. Soc.*, **1939**, 391; Lehmann, *Ber.*, **71**, 1874 (1938); Butz *et al.*, *J. Org. Chem.*, **5**, 171 (1940); Backer *et al.*, *Rec. trav. chim.*, **53**, 525 (1934); **58**, 761 (1939); **60**, 557 (1941).

[144] In regard to the diene synthesis of hydroxylated α-naphthoquinones and their conformity to the general rule consult Fieser and Dunn, *J. Am. Chem. Soc.*, **59**, 1016 (1937); see also Werntz, *ibid.*, **57**, 204 (1935); Arbuzov and Nikanorov, *J. Gen. Chem.* (*U. S. S. R.*), **10**, (72), 649 (1940); *Chem. Zentr.*, **1940,II**, 2740.

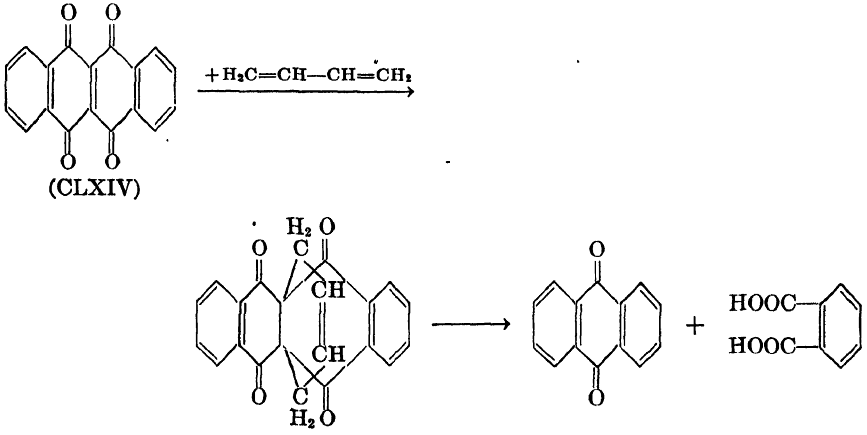
coholic alkali solution to 1,1,3-trimethyl-1,4-dihydroanthraquinone (CLXIII).[142,145]



(CLXII)

(CLXIII)

The following instance illustrates the types of products which may be obtained by the reaction of dienes with quinones. Naphthacenediquinone (CLXIV), which adds simple dienes smoothly, reacts with butadiene to form the interesting tetraketone type (CLXV).[146]



(CLXIV)

(CLXV)

Alkaline hydrolysis of the adduct in the presence of air gives anthraquinone and *o*-phthalic acid, thus proving its structure.[147]

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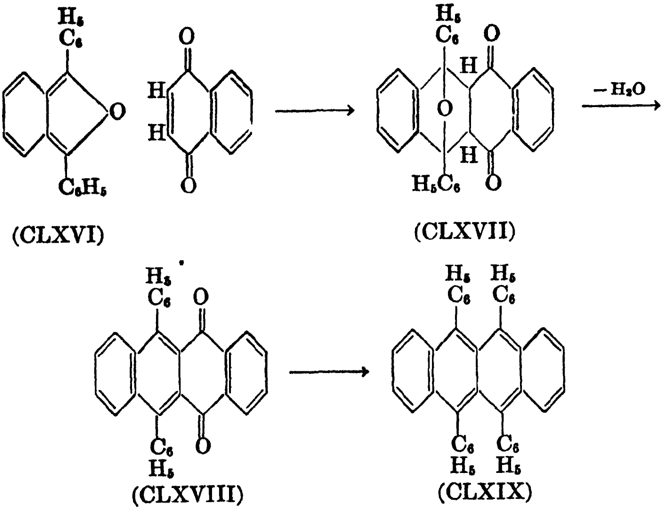
[145] Fieser and Weighard, *J. Am. Chem. Soc.*, **62**, 153 (1940). Fieser, *Science*, **91**, 31 (1940).

[146] Fieser and Dunn, *J. Am. Chem. Soc.*, **58**, 1054 (1936).

[147] For a second, likewise illuminating, example see Zahn, *Ber.*, **67**, 2075 (1934).

Dienes of the type *α, α′-diaryl-β,β′-benzofuran* (CLXVI) (p. 428, 493 ff.) also show a normal behavior in their reaction with quinones. The adducts are easily converted to polynuclear aromatic compounds. The addition product (CLXVII) of α,α′-diphenyl-β,β′-benzofuran (CLXVI) and α-naphthoquinone loses the elements of water, a reaction which is typical of this class. It is thereby transformed into a diphenylnaphthacenequinone (CLXVIII).

The quinone (CLXVIII) reacts with phenylmagnesium bromide to give a carbinol which may be reduced to 9,10,11,12-tetraphenylnaphthacene (rubrene) (CLXIX).[148,149]



(CLXVI) (CLXVII)

(CLXVIII) (CLXIX)

The diene synthesis of 1-vinylcyclohexene (CLXX) with *p*-benzoquinone results in compounds with three or five fused six-membered rings. The addition produces either 1,4-diketodecahydrophenanthrene (CLXXI) or 9,10-diketooctahydro-1,2,5,6-dibenzanthracene (CLXXII),[150] depending on the relative proportion of the components and the reaction conditions that are employed.

In a similar manner 1-vinylcyclooctene has been added to naphthoquinone and benzoquinone to give polymethylene anthraquinones.[151]

The diene synthesis with quinones offers many possibilities for the synthesis of new polynuclear anthracene derivatives, especially when highly substituted derivatives of cyclopentadienone are employed (page 459).

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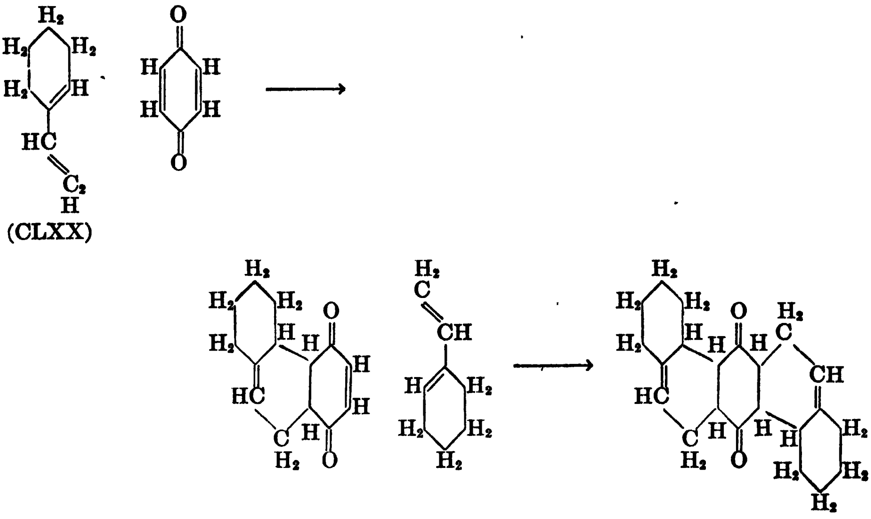
[148] Dufraisse and Compagnon, *Compt. rend.*, **207**, 585 (1938).

[149] Bergmann, *J. Chem. Soc.*, **1938**, 1147.

[150] Cook and Lawrence, *J. Chem. Soc.*, **1938**, 58.

[151] Barker and van der Bij, *Rec. trav. chim.*, **62**, 561 (1943); *Chem. Abstracts*, **39**, 3529 (1945).

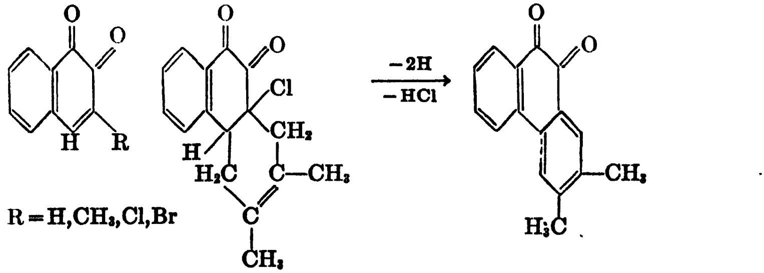


(CLXX)

(CLXXI) (CLXXII)

(*d*) *Phenanthrene, Chrysene, Picene, and Cyclopentenophenanthrene Series; Synthesis of Steroids.* The most important stimulus for the synthesis of this group arises from the endeavor to prepare sterol and compounds which are closely related to it. Synthetic experiments in the morphine series have also encouraged new work in this field.

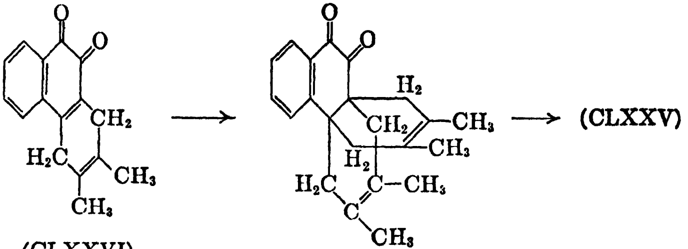
In view of the success which has attended the use of *p*-benzoquinone and α-naphthoquinone as dienophiles it is only natural to investigate the synthetic possibilities of β-naphthoquinone (CLXXIII) (R = H). The use of this compound should result in a partially hydrogenated phenanthrenequinone. However, such a synthesis fails because of the sensitivity of β-naphthoquinone.



R = H, CH_3, Cl, Br

(CLXXIII) (CLXXIV) (CLXXV)

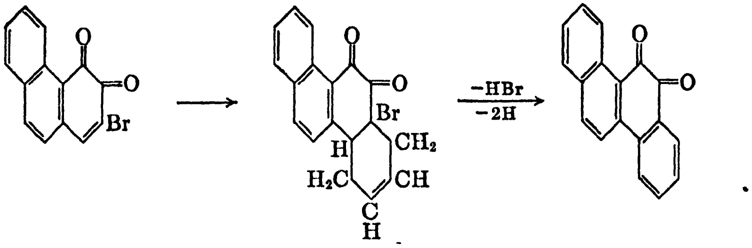
The fact that a substituent in the 3 position increases the stability of β-naphthoquinone considerably, without noticeably decreasing the activity of the double bond toward addition, has made possible the synthesis of numerous compounds of this series.[138,152] 3,6-Dimethyl-β-naphthoquinone adds dienes in the expected manner with the formation of hydrogenated phenanthrene derivatives with angular methyl groups. A halogen in the 3 position[153] likewise exerts a stabilizing influence on the β-naphthoquinone molecule and makes possible its use in the diene synthesis. This fact is of great value in the synthesis of phenanthrene derivatives; for example, a normal addition product (CLXXIV) is formed by the addition of 2,3-dimethylbutadiene to 3-chloro-β-naphthoquinone. The adduct is converted into 2,3-dimethylphenanthraquinone (CLXXV) by the elimination of hydrogen halide followed by oxidation. It is worthy of mention that if the adduct (CLXXIV) is allowed to react with excess 2,3-dimethylbutadiene for a long period of time a tetracyclic product (CLXXVII) is formed by the elimination of hydrochloric acid and the addition of a second diene molecule to the newly formed double bond of compound CLXXVI. By heating above its melting point this compound



(CLXXVI) (CLXXVII)

undergoes a thermal dissociation, and simultaneous dehydrogenation to 2,3-dimethylphenanthraquinone (CLXXV).[154]

The phenanthraquinone analogue, chrysene-5,6-quinone (CLXXIX),



(CLXXVIII) (CLXXIX)

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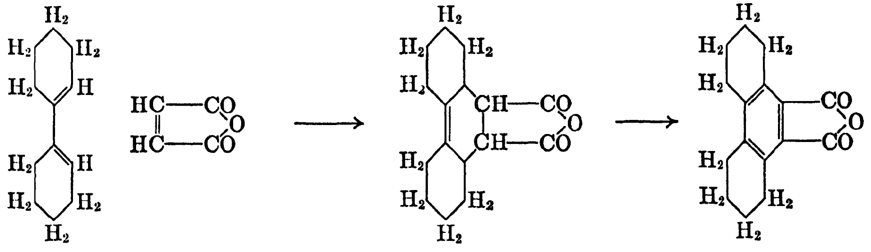
[152] Fieser and Dunn, *J. Am. Chem. Soc.*, 59, 1016, 1021, 1024 (1937).

[153] 4-Halogen-1,2-naphthoquinones are of little use in the diene synthesis. 3,4-Dihalogenonaphthoquinone is added only with difficulty [Fieser and Dunn, *J. Am. Chem. Soc.*, 59, 1016 (1937)].

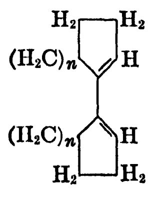
[154] Fieser and Dunn, *J. Am. Chem. Soc.*, 59, 1021 (1937).

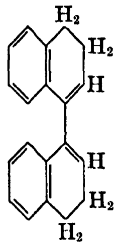
may be prepared by the addition of 2-bromophenanthrene-3,4-quinone (CLXXVIII) to butadiene.[155]

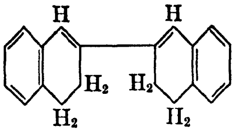
An alternate route to the phenanthrene series is found in the interaction of 1,1′-octahydrobiphenyl (CLXXX) with various dienophiles. The products are hydrogenated phenanthrene derivatives.[156] For example, dodecahydrophenanthrenedicarboxylic anhydride (CLXXXI), which is formed when maleic anhydride is the dienophile, is dehydrogenated to the anhydride of 1,2,3,4,5,6,7,8-octahydrophenanthrenedicarboxylic acid (CLXXXII). This variation of the diene synthesis has proved exceptionally fruitful. In place of maleic anhydride numerous other dienophiles such as *p*-benzoquinone, *α*-naphthoquinone, acrolein, and cinnamic acid may be substituted.[157] Moreover, the procedure for the preparation of 1,1′-octahydrobiphenyl (CLXXX) is capable of considerable variation.

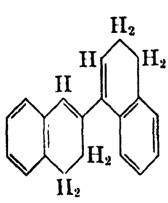

(CLXXX) (CLXXXI) (CLXXXII)

The general procedure for the synthesis of these derivatives consists of a bimolecular reduction of a cyclic ketone to a pinacol-like diol which is transformed into a bicyclic diene by the elimination of the elements of water. Numerous dienes of the general formula CLXXXIII have been


(CLXXXIII)


(CLXXXIV)


(CLXXXV)


(CLXXXVI)

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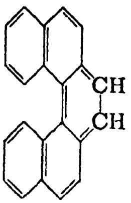
[155] Fieser and Dunn, *J. Am. Chem. Soc.*, **59**, 1024 (1937); also other variations in this work.

[156] Barnett and Lawrence, *J. Chem. Soc.*, **1935**, 1104; U. S. Patent, 2,092,902; *Chem. Zentr.*, **1936,I**, 4213; *Chem. Abstracts*, **31**, 7889 (1937); British Patent, 438,894; *Chem. Zentr.*, **1936,I**, 4213; *Chem. Abstracts*, **30**, 2989 (1936). Gruber and Adams, *J. Am. Chem. Soc.*, **57**, 2555 (1935); **60**, 2792 (1938). Weizmann, Bergmann, and Berlin, *ibid.*, **60**, 1331 (1938). Backer *et al.*, *Rec. trav. chim.*, **58**, 761 (1939); **60**, 557 (1941).

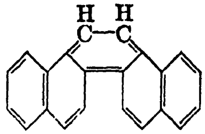
[157] Bergmann *et al.*, *J. Org. Chem.*, **8**, 179 (1943).

prepared in this way. Many combinations are thus available through a suitable choice of components. Bergmann, however, has shown that cyclohexene and derived hydrocarbons do not undergo the diene synthesis with bicyclohexenyl. On the contrary, 1-methylcyclopentene and indenes yield the corresponding adducts with this diene.[158]

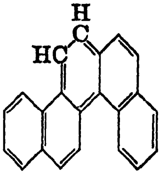
The three 1-bisdialins (CLXXXIV, CLXXXV, and CLXXXVI) and maleic anhydride yield products which may be considered as derivatives of 3,4,5,6-dibenzophenanthrene (CLXXXVII), 1,2,7,8-dibenzophenanthrene (picene) (CLXXXVIII), and 1,2,5,6-dibenzophenanthrene (CLXXXIX), respectively.[159]



(CLXXXVII)

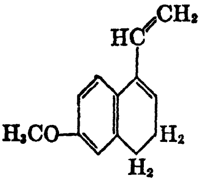


(CLXXXVIII)

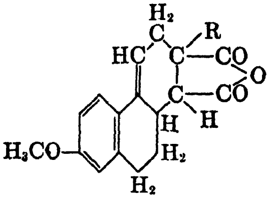


(CLXXXIX)

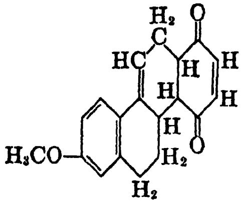
Another method of synthesis of phenanthrene derivatives is that in which the following are used: 1-vinyl-6-methoxy-3,4-dihydronaphthalene (CXC) or 1-ethynyl-6-methoxy-3,4-dihydronaphthalene (CXCV), in which the diene system C═C—C═C or the enyne system C═C—C≡C, re-



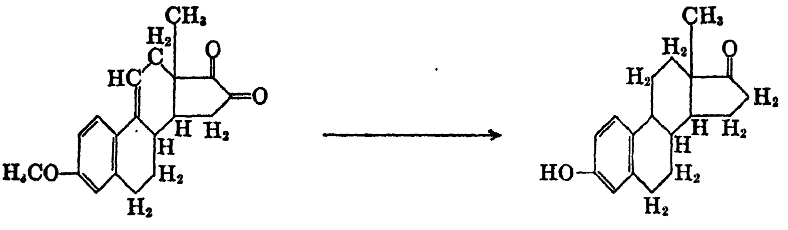
(CXC)



(CXCI)



(CXCII)



(CXCIII) (CXCIV)

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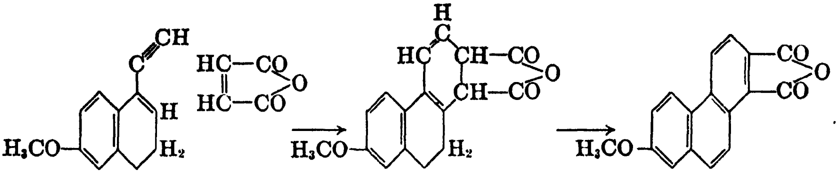
[158] Bergmann *et al.*, *J. Org. Chem.*, 9, 352 (1944).
[159] Weidlich, *Ber.*, 71, 1203 (1938).

spectively, is shared by the ring and side chain. A general method with many possible modifications is now available for preparing the starting materials. It depends on the reaction of a Grignard or other organometallic compound of acetylene with cyclic ketones.

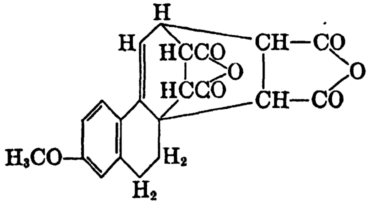
The use of the first of these dienes in conjunction with acyclic dienophiles leads to phenanthrene derivatives; with cyclohexene dienophiles, to chrysene; and with cyclopentene dienophiles, to cyclopentenophenanthrene derivatives. The addition of maleic anhydride, *p*-benzoquinone, and 1-methyl-1-cyclopentene-4,5-dione to 1-vinyl-6-methoxy-3,4-dihydronaphthalene (CXC)[160] to yield CXCI (R = H) CXCII, and CXCIII may be cited as examples.

The tetracyclic diketophenol ether (CXCIII) has been degraded by the usual methods to the ketophenol (CXCIV), which is structurally identical with the hormone estrone and differs from the natural product only in its spatial configuration. It shows the same physiological activity although in a smaller degree. The addition product (CXCI, R = CH_3), from methylmaleic anhydride and CXC may also be converted to estrone.[161]

The use of 1-vinyl-6-methoxy-3,4-dihydronaphthalene (CXC) in the diene synthesis is only an extension of previous work. However, 1-ethynyl-6-methoxy-3,4-dihydronaphthalene (CXCV) presents a new factor in the enyne system, $>C{=}C{-}C{\equiv}C{-}$. According to the explanation given in the introduction of this article (see p. 390), a system which has



(CXCV) (CXCVI) (CXCVII)



(CXCVIII)

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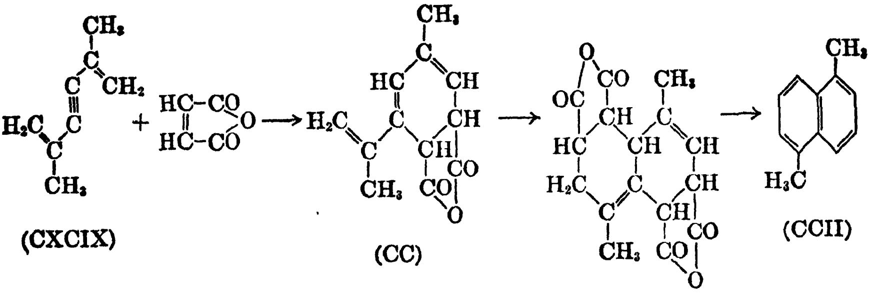
[160] Dane *et al.*, *Ann.*, **532**, 29, 39 (1937); **536**, 183, 195 (1938); **537**, 246 (1939); *Angew. Chem.*, **52**, 36, 655 (1939). See also Bockemüller, *ibid.*, **51**, 188 (1938), and Tahsin-Dikmen, Dissertation, Würzburg (1936).

[161] Breitner, *Med. Chem.*, **4**, 317 (1942); *Chem. Abstracts*, **38**, 4953 (1944).

such a combination of unsaturated elements adds dienophiles in the normal manner (*i.e.*, by 1,4 addition), but with a simultaneous rearrangement of the hydrogen atom. Thus, in agreement with these rules 7-methoxytetrahydrophenanthrene-1,2-dianhydride (CXCVI) is formed under very mild conditions from 1-ethynyl-6-methoxy-3,4-dihydronaphthalene and maleic anhydride.[162]

The adduct (CXCVI) has been dehydrogenated to 7-methoxyphenanthrene-1,2-dicarboxylic anhydride (CXCVII). Moreover, as a diene it adds a second molecule of maleic anhydride with the formation of a tetracarboxylic acid anhydride (CXCVIII). Both transformations permit no doubt as to the constitution of the adduct (CXCVI) from 1-ethynyl-6-methoxy-3,4-dihydronaphthalene and maleic anhydride.

It is to be expected that the diene synthesis with enyne systems will acquire considerable value as a preparative method. The first step in this direction is the addition reaction of dienynes containing the characteristic group $>C{=}C{-}C{\equiv}C{-}C{=}C<$. The behavior of such a system is comparable with that of the system $>C{=}C{-}C{\equiv}C{-}$. Thus the addition of 2 moles of maleic anhydride to 2,5-dimethyl-1,5-hexadien-3-yne (CXCIX) gives an adduct which belongs to the naphthalene series (CCI). Dehydrogenation and decarboxylation with palladium-charcoal gives 1,5-dimethylnaphthalene (CCII).[163]


(CXCIX) (CC) (CCI) (CCII)

It is to be assumed that the adduct is the result of two consecutive diene syntheses which take place in the dienyne system. First the enyne grouping reacts according to the scheme of 1,4 addition, with simultaneous rearrangement of hydrogen as given for 1-ethynyl-6-methoxy-3,4-dihydronaphthalene (CXCV). The compound (CC) which results still contains the triene system $>C{=}C{-}C{=}C{-}C{=}C<$, and thus permits 1,4 addition of a second molecule of maleic anhydride with the formation of the naphthalene nucleus.[164] Benzoquinone has also been added to CXCIX to give a chrysene diquinone.[165]

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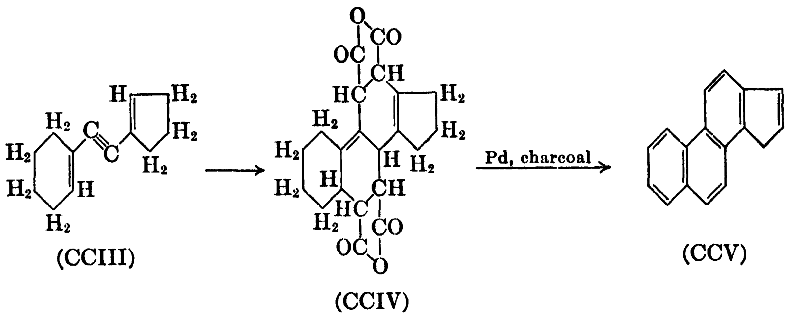
[162] Dane *et al.*, *Ann.*, **532**, 39 (1937); **536**, 183 (1938). See Breitner, *Chem. Abstracts*, **38**, 4953 (1942).

[163] Butz *et al.*, *J. Org. Chem.*, **5**, 379 (1940); *J. Am. Chem. Soc.*, **62**, 995 (1940).

A second instructive example of this process is the synthesis of cyclopentenophenanthrene from 1-cyclohexenyl-1-cyclopentenylacetylene (CCIII). In a similar way 2 moles of maleic anhydride are attached to



(CCIII) (CCIV) (CCV)

this hydrocarbon with the formation of the dianhydride (CCIV), which can be dehydrogenated and decarboxylated to cyclopentenophenanthrene (CCV), the parent body of the steroids.[163] Dicyclohexenylacetylene gives a chrysene derivative under the same conditions,[166] while cyclopentenylisopropenylacetylene gives 8-methyl-3,4-trimethylene-1,2,3,5,6,7-hexahydronaphthalene-1,2,5,6-tetracarboxylic anhydride.[167]

Cyclopentenophenanthrene may be prepared in another manner by the aid of the diene synthesis. The principles of this method were discussed in a previous section.[131,168]

The synthesis of certain hydrogenated phenanthrenecarboxylic acids is of interest because the angular carboxyl group on carbon atom 13 occurs in the same position as the amino ethane chain in morphine (CCVIII). The new hydrophenanthrenecarboxylic ester is obtained by the addition of diene hydrocarbons to 1-dihydro-1-naphthoic ester and its derivatives; for example, 3-methoxy-5,8,9,10,13,14-hexahydrophenanthrene-13-carboxylic ester (CCVII) is obtained from 7-methoxy-3,4-dihydro-1-naphthoic ethyl ester (CCVI) and butadiene.[169]

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[164] The location of one of the two double bonds in the adduct (CCI) was assumed to be in another position by Butz and his co-workers [Butz and Joskel, *J. Am. Chem. Soc.*, **63**, 3344 (1941); **64**, 1311 (1941)].

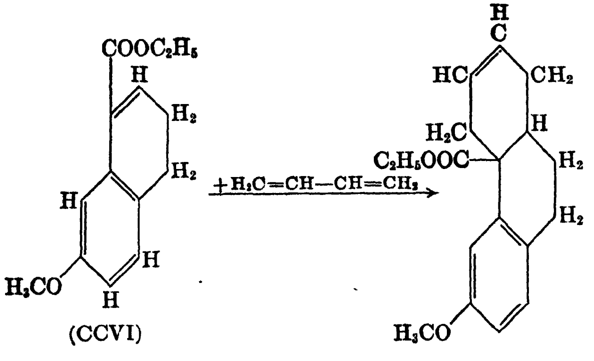
[165] Butz, Gaddes, and Butz, *J. Am. Chem. Soc.*, **69**, 924 (1947).

[166] Butz, U.S. Patent, 2,387,830; *Chem. Abstracts*, **40**, 1177 (1946).

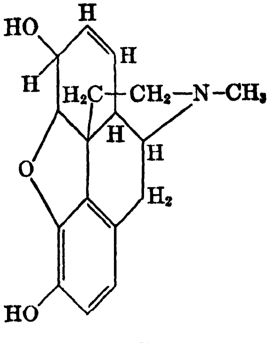
[167] Butz, U.S. Patent, 2,405,540 (1946); *Chem. Abstracts*, **41**, 486 (1947).

[168] Compare the above procedure with the synthesis of the naphthalene series which was given on p. 426 ff.

[169] Fieser and Holmes, *J. Am. Chem. Soc.*, **58**, 2319 (1936). Concerning further synthesis of a similar nature see Fieser and Holmes, *ibid.*, **60**, 2548 (1936) and Fieser and Price, *ibid.*, **58**, 1838 (1936). The constitution of the adduct is conclusively proved in these experiments.



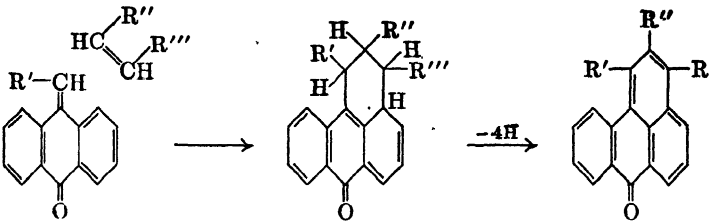
(CCVI) (CCVII)



(CCVIII)

(*e*) *Benzanthrone Series.* The fact that conjugated systems of double bonds are still capable of the diene synthesis if one of the two double bonds is part of an aromatic system plays a decisive role in the formation of compounds of the benzanthrone series and analogous higher condensation products of the anthracene series. Methyleneanthrone (CCIX) ($R' = H$) and its various derivatives, such as benzilideneanthrone ($R' = C_6H_5$) and β-anthraquinonylmethyleneanthrone ($R' = \beta\text{-}C_{14}H_7O_2$), function as diene components in these syntheses. These compounds react with surprising ease with a variety of dienophiles, α,β-unsaturated carboxylic acids, aldehydes, ketones, quinone, naphthoquinone,[170] indene,[171] and allyl alcohol.[172]

The partially hydrogenated compounds (CCX) which are formed in the reaction are transformed readily into the aromatic parent substance (CCXI). This is best accomplished by the use of a solvent such as nitrobenzene, which is a mild oxidizing agent. Among the great number of



(CCIX) (CCX) (CCXI)

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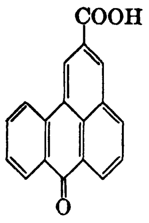
[170] I. G. Farbenindustrie A.-G. and Scheyer, German Patents, 591,496, 597,325. Clar, *Ber.*, 69, 1686 (1936); German Patent, 619,246. du Pont de Nemours, U. S. Patent, 2,136,998. The significance of R″ and R‴ depends on the general characteristics of the dienophile component; compare the work of Allen, Bell, Bell, and VanAllan, *J. Am. Chem. Soc.*, 62, 656 (1940).

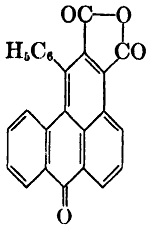
[171] Swain and Todd, *J. Chem. Soc.*, 1942, 626.

[172] Shvaleva, *Uchenye Zapiski Kazan. Gosudarst. Univ. im. V. I. Ul'yanova-Lenina*, 101, No. 3, *Sbornik Studencheskirkh Rabot*, No. 2, 55 (1941); *Chem. Abstracts*, 40, 568 (1946).

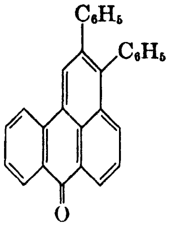
compounds which may be obtained conveniently by this procedure are benzanthrone-*Bz*-2-carboxylic acid (CCXII), from methyleneanthrone and fumaric acid, with simultaneous elimination of a mole of carbon dioxide; *Bz*-1-phenylbenzanthrone-*Bz*-2-*Bz*-3-anhydride (CCXIII), from benzilideneanthrone and maleic anhydride; *Bz*-2-*Bz*-3-diphenylbenzanthrone (CCXIV), from methyleneanthrone and stilbene; and finally the condensation product (CCXV), from methyleneanthrone and α-naphthoquinone.



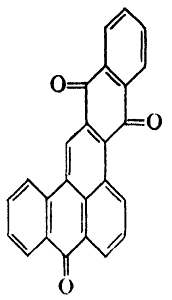
(CCXII)



(CCXIII)

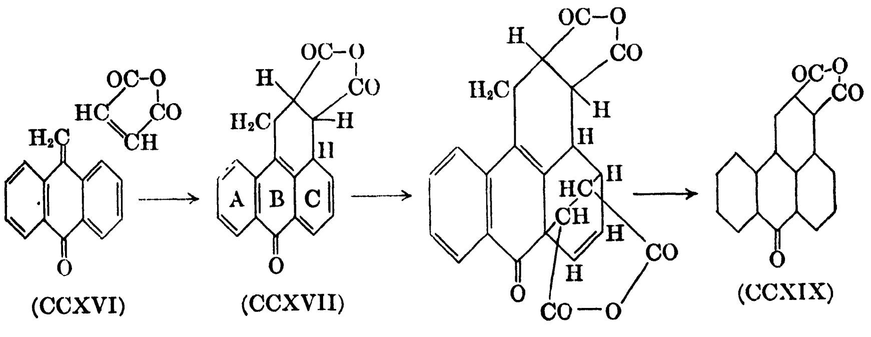


(CCXIV)



(CCXV)

Clar[173] has studied the reaction of methyleneanthrone (CCXVI) with maleic anhydride. By maintaining suitable reaction conditions, the primary addition product (CCXVII) adds a second molecule of maleic anhydride to the newly formed system of conjugated double bonds and leads to the endo compound (CCXVIII) which has a succinic anhydride bridge. The bridge is easily eliminated from the adduct (CCXVIII) by known methods[174] and is transformed by simultaneous dehydrogenation into the anhydride of benzanthrone-*Bz*-2-*Bz*-3-dicarboxylic acid (CCXIX). This



(CCXVI) (CCXVII) (CCXVIII) (CCXIX)

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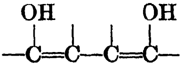
[173] In non-oxidizing solution media, as for example acetic acid; Clar, *Ber.*, **69**, 1686 (1936).

[174] Compare the diene synthesis in the ergosterol and anthracene series.

may be also synthesized by the action of maleic anhydride on methyleneanthrone in boiling nitrobenzene.

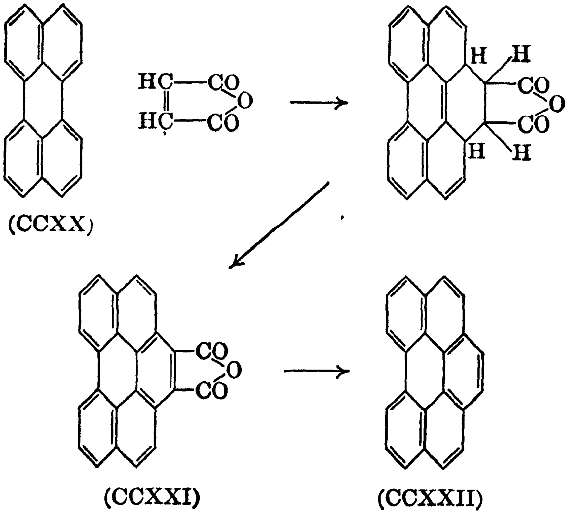
Bergmann has found that nitrobenzene dehydrogenates only the adducts which are capable of double ortho enolization as, for example, those of maleic anhydride and quinone. This reaction appears of general application to those systems which can have the following grouping[175] (see also pages 402 and 458).



$$-\overset{\text{OH}}{\overset{|}{\text{C}}}=\overset{|}{\text{C}}-\overset{|}{\text{C}}=\overset{\text{OH}}{\overset{|}{\text{C}}}-$$

(*f*) *Pyrene, 1,12-Benzoperylene, Coronene, and Dibenzocoronene Series.* In both the preceding sections diene syntheses were discussed in which only half of the double bond system was shared by an aromatic nucleus. The question is raised whether diene syntheses can occur in a purely aromatic system. Experience has shown that the simple aromatic compounds of the benzene, naphthalene, biphenyl, and phenanthrene series are not capable of such additions. The first representative which adds dienophile components according to the scheme of the diene synthesis has at least three linearly fused nuclei. Since the conjugated system which reacts lies in a ring, a compound with a bridge results. This type of compound will be discussed in another section (see page 485 ff).

A second group of compounds with purely aromatic character which are capable of undergoing the diene synthesis and in which the conjugated double bonds are shared by two nuclei is encountered in the higher con-



(CCXX)

(CCXXI)

(CCXXII)

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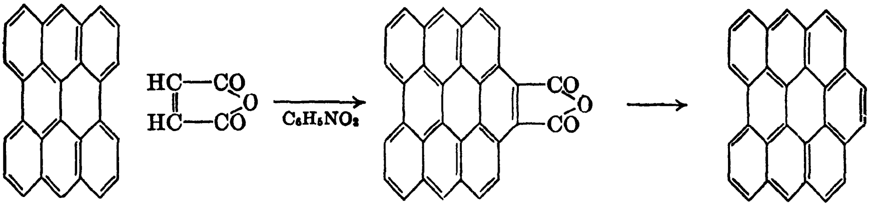
[175] Bergmann, *J. Am. Chem. Soc.*, 64, 176 (1942)

densed types such as the benzanthrene and the perylene series. The latter has been investigated repeatedly in this connection.[176]

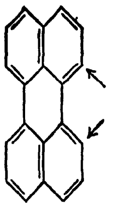
The addition of dienophilic components occurs in the 1,12 position of the perylene system and, in weakly oxidizing media, the primary product (not isolated) is converted directly into the 1,12-benzoperylene series. The presence of hydrogen in the 1,12 position is a necessary condition for the addition. It is eliminated together with the hydrogen of the maleic anhydride during dehydrogenation. The course of the reaction is illustrated by the addition of maleic anhydride to perylene (CCXX).

The 1,12-benzoperylene-*Bz*-1-*Bz*-2-dicarboxylic anhydride (CCXXI) which is formed in 80 to 90% yield from perylene (CCXX) and maleic anhydride may be decarboxylated to 1,12-benzoperylene (CCXXII).

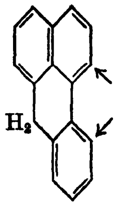
It is not surprising that systems which contain the perylene skeleton, but are more highly condensed, also add dienophiles according to the same mechanism. For example, mesonaphthodianthrene (CCXXIII) reacts with maleic anhydride in boiling nitrobenzene with simultaneous dehydrogenation to give 2,3,4,5-(*vic*-diperi)dibenzocoronene anhydride (CCXXIV) in quantitative yield. Decarboxylation results in the production of 2,3,4,5-dibenzocoronene (CCXXV).[177–179]



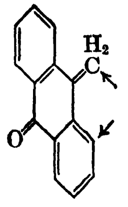
(CCXXIII) (CCXXIV) (CCXXV)



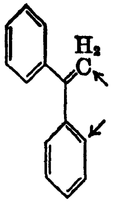
(CCXX)



(CCXXVI)



(CCXXVII)



(CCXXVIII)

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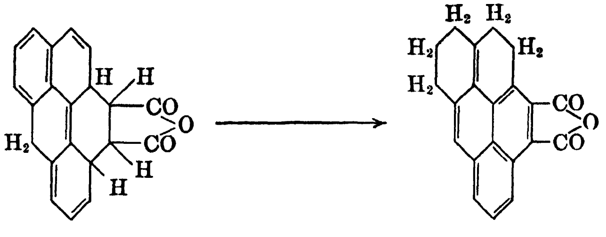
[176] I. G. Farbenindustrie A.-G., Köberle and Anton, German Patent, 651,677. Clar, *Ber.*, 65, 846 (1932); 73, 351 (1940). Zincke *et al.*, *ibid.*, 73, 1187 (1940).

[177] Scholl and Meyer, *Ber.*, 67, 1236 (1934).

[178] A second case, *cf.* Clar, *Ber.*, 65, 846 (1932).

[179] A synthesis of coronene by the diene synthesis has been described recently by Newman, *J. Am. Chem. Soc.*, 62, 1683 (1940).

Less highly condensed nuclei containing only part of the perylene skeleton such as benzanthrene (CCXXVI), methyleneanthrone (CCXXVII) diphenylethylene (CCXXVIII), and phenanthrene should also be considered. The reaction of methyleneanthrone (CCXXVII) with dienophiles has already been discussed. "Contraction" of perylene to phenanthrene or to the biphenyl type completely destroys the additive power of the system. Benzanthrene (CCXXVI) adds maleic anhydride very smoothly with the formation of a partially hydrogenated pyrene derivative (CCXXIX) which is stabilized by intramolecular rearrangement of the hydrogen and formation of CCXXX.[180]



(CCXXIX) (CCXXX)

C. Bridged Ring Systems

This type of compound can be secured by the diene synthesis only when the conjugated double bonds of the diene component are part of a ring. The dienophile partner may be cyclic or acyclic.

(1) Bicyclo-[2.2.1]-heptane Series. Cyclopentadiene and its derivatives are especially favorable compounds for the diene synthesis. This is probably due to the fact that in conjugated systems of double bonds the cyclopentadiene system shows no freedom of rotation; in contrast, the acyclic dienes have complete freedom of rotation[181] and cyclic dienes with more than 5 atoms in the ring show some distortion. The various cyclic and acyclic dienes react with the same dienophile at different rates. If the degree of substitution is similar, the cyclopentadiene system reacts the most readily.

There is a second property that is characteristic of cyclopentadiene. The monomeric form of the hydrocarbon changes very easily into a dimer (CCXXXI), a reaction which corresponds completely to the dimerizations of other cyclic and acyclic diene hydrocarbons such as butadiene, isoprene, and 1,3-cyclohexadiene. However, of all such dimers, only dicyclopentadiene is again dissociated into the monomer by the application of moderately low temperatures (100° to 150°C.). An analogous dissociation of the dimers of other dienes occurs only at considerably higher temperatures.

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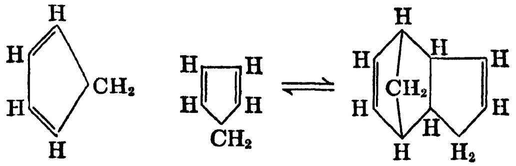
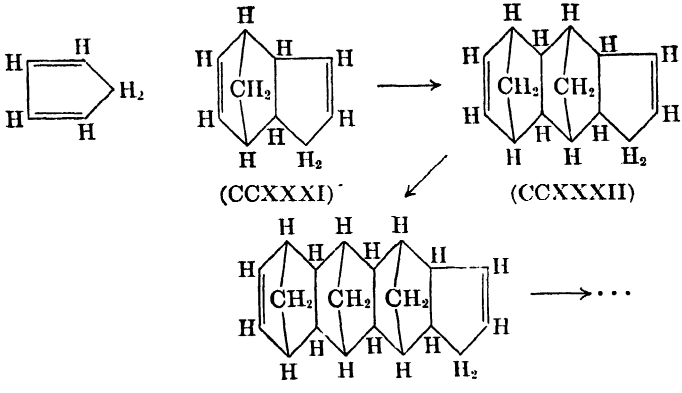
[180] Clar, *Ber.*, 65, 1425 (1932).

[181] For ex ceptional cases, *e.g.*, 2,3-di-*tert*-butyl-1,3-butadiene, see p. 382.



(CCXXXI)

It is, therefore, apparent why cyclopentadiene adds to slowly reacting olefin partners (*e.g.*, vinyl acetate, vinyl chloride) at elevated temperatures to give excellent yields, while the same compounds give poor yields with butadiene and cyclohexadiene. In the last two cases the formation of a stable dimer prevents the desired reaction. In order to account for the highly successful results obtained with cyclopentadiene, it must be assumed that the dienophile component possesses a certain marked tendency to react with this diene. Otherwise the free monomer formed from the dimer at higher temperatures would be lost through a concurrent reaction. This depends upon the fact that dicyclopentadiene (CCXXXI) is also capable of a diene synthesis with the monomer. The resulting trimer (CCXXXII) can still add monomeric cyclopentadiene to form a tetramer (CCXXXIII), which can then react to form a pentamer, and so forth.



(CCXXXI) (CCXXXII)

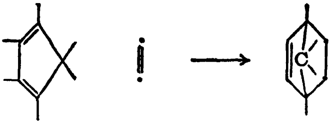
(CCXXXIII)

The higher polymers of cyclopentadiene are considerably more stable to high temperatures than is the dimer. Hence the use of high temperatures results in the removal of the monomeric hydrocarbon. Therefore, this reaction, which has been studied thoroughly,[182] should be kept in mind when cyclopentadiene is used in preparative work.

[182] Alder and Stein, *Angew. Chem.*, **47**, 837 (1934); this includes a compilation of earlier references.

Diene syntheses with cyclopentadiene have resulted in the formation of compounds of the bicyclo-[2.2.1]-heptane series, to which the important and thoroughly studied natural products like camphor and santene belong. Until the advent of the diene synthesis such substances were secured only by the use of the traditional methods which were usually difficult and tedious, however ingeneous.

Compounds of the type CCXXXIV, which can now be obtained in many variations, are of importance in considering a general study of the diene synthesis, because of the new possibilities they disclose. The relationship between ring strain and energy content, ring strain and reactivity, the dependence of intramolecular rearrangements on ring structure, questions concerning the steric course of reactions which take place in these ring systems—all these considerations have stimulated a thorough study of the diene synthesis with the cyclopentadiene type. In this section, therefore, the whole field is particularly well covered.



(CCXXXIV)

(*a*) *Cyclopentadiene and Its Derivatives as Diene Components.* The parent substance in this group of dienes, cyclopentadiene, has been added to all olefin and acetylene types that are commonly used in the diene synthesis.[183] As would be expected, α,β-unsaturated carbonyl compounds also prove especially serviceable here. If the additive unsaturated centers are not inactivated by large substituents, the addition proceeds at room temperature in dilute solution with vigorous evolution of heat. In some cases heating with or without solvents is required to produce the desired result. To the first group belong such substances as *p*-benzoquinone,[90,184] α-naphthoquinone,[90,184] maleic acid and its anhydride, imide, and esters,[70,185] fumaryl chloride,[186] maleonitrile and fumarónitrile,[187,188] citraconic and itaconic anhydrides,[70,189] acrylic acid[70,189] and its esters and nitrile,[188,189] acrolein,[70,189] methyl vinyl ketone,[190] phenyl vinyl ketone,[111] acetylenedicarboxylic acid and its esters,[191] and propiolic acid.[192] These examples include only the main types. No claim to completeness is intended. With more highly substituted derivatives, such as the substituted quinones,[187] the anhydrides of pyrocinchonic[193] and dibromomaleic acid,[194] crotonic acid[189] and its nitrile,[195] tetrolic acid,[196] and β-nitrostyrene,[197] the use of higher temperatures, though not always necessary, is usually recommended.

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[183] Alder (foot-note 1), "Die Methoden der Diensynthese", p. 3097.

[184] Albrecht, *Ann.*, **348,** 31 (1906). Alder and Stein, *Ann.*, **501,** 247 (1933).

[185] Diels and Alder, *Ann.*, **478,** 137 (1930). Alder and Stein, *ibid.*, **514,** 1 (1934). I. G. Farbenindustrie A.-G., French Patent, 861,668.

[186] Alder and Stein, *Ann.*, **514,** 209 (1934).

[187] Blomquist and Winslow, *J. Org. Chem.*, **10,** 149 (1945).

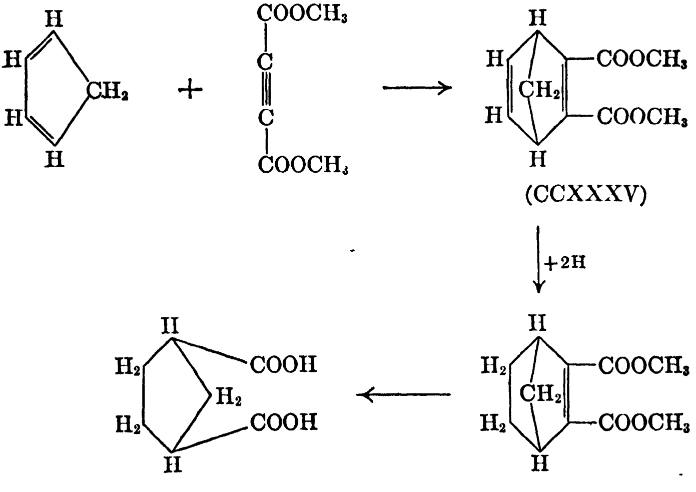
[188] Moury, *J. Am. Chem. Soc.*, **69,** 573 (1947).

[189] Alder and Stein, *Ann.*, **514,** 197 (1934).

[190] Wolfe, U.S. Patent, 2,217,632 (1940); *Chem. Abstracts*, **35,** 1069 (1941). Miller and Bradley, U.S. Patent, 2,382,803 (1945); *Chem. Abstracts*, **39,** 4892 (1945).

The course of the reaction (addition in the 1,4 position with formation of bicyclo-[2.2.1]-heptane ring systems) is clearly demonstrated in the great majority of known cases. As an example, consider the addition of cyclopentadiene to methyl acetylenedicarboxylate. This reaction proceeds at room temperature in dilute solution to give a quantitative yield of methyl 3,6-endomethylene-3,6-dihydrophthalate (CCXXXV). The partial catalytic hydrogenation of the adduct gives methyl 3,6-endomethylene-3,4,5,6-tetrahydrophthalate (CCXXXVI). By saponification of CCXXXVI, followed by oxidative degradation, cyclopentane-1,3-dicarboxylic acid (CCXXXVII) is obtained.[191,194]

The esters of azodicarboxylic acid, ROOC—N=N—COOR, add to



(CCXXXV)

(CCXXXVII) (CCXXXVI)

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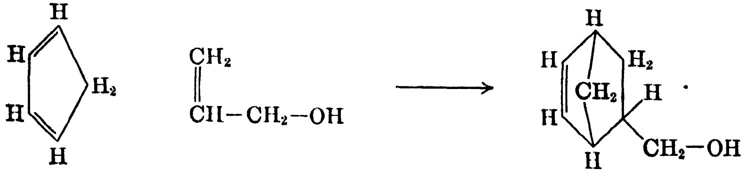
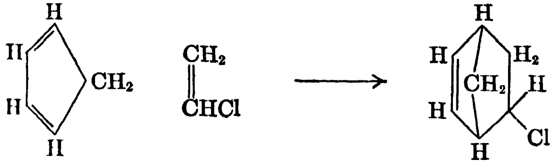
[191] Diels and Alder, *Ann.*, **490**, 236 (1931).
[192] Alder and Stein, *Ann.*, **525**, 183 (1936).
[193] Diels and Alder, *Ber.*, **62**, 554 (1929).
[194] Diels and Alder, *Ann.*, **478**, 137 (1930).
[195] I. G. Farbenindustrie A.-G., French Patent, 37,498; *Chem. Zentr.*, **1931**,I, 1520; *Chem. Abstracts*, **25**, 2436 (1931).
[196] Diels and Olsen, *J. prakt. Chem.*, **156**, 285 (1940).
[197] Allen and Bell, *J. Am. Chem. Soc.*, **61**, 521 (1939). Allen, Bell, and Gates, *J. Org. Chem.*, **8**, 373 (1943).

cyclopentadiene with great ease at the —N═N— double bond and by the same mechanism. A heterocyclic six-membered ring with a $-CH_2-$ bridge results. This reaction will be considered in a later section (see page 505).

In addition to the α,β-unsaturated carbonyl compounds, which are prominent because of their great additive capacity, some weaker olefin components will also react smoothly with cyclopentadiene. The reasons for this exclusive position of cyclopentadiene have already been pointed out in the introduction to this chapter. Such olefins are vinylacetic acid, $CH_2{=}CH{-}CH_2COOH$,[198] allylnitrile, $CH_2{=}CH{-}CH_2CN$,[85,199] the allyl halogen compounds, $CH_2{=}CH{-}CH_2hal.$,[198] allylamine, $CH_2{=}CH{-}CH_2NH_2$,[198] and allyl alcohol, $CH_2{=}CH{-}CH_2OH$,[198] all of which add cyclopentadiene smoothly at elevated temperatures.



Further, the esters of the hypothetical alcohol, vinyl alcohol, especially vinyl acetate[85,199] and vinyl formate,[85,199] as well as the halogen substitution products of ethylene,[85,199] such as vinyl chloride and di- and trichloroethylene, undergo a diene synthesis with cyclopentadiene.



It should be noted that adducts of cyclopentadiene including dicyclopentadiene are capable of adding alcohols and phenols.[128,200–204] During the addition, however, a Wagner-Meerwein rearrangement takes place and a derivative of the *exo* isomer instead of the *endo* isomer is obtained.[205]

As would be expected, the reactivity of cyclopentadiene toward the halogenated ethylenes decreases with increased substitution. Thus, trichloroethylene adds at an elevated temperature to give only a moderate yield of adduct, while the velocity of addition of tetrachloroethylene is diminished so much that the polymerization of cyclopentadiene becomes the main reaction.

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[198] Alder and Windemuth, *Ber.*, **71**, 1939 (1938), includes other cases of this type; U. S. Patent, 2,352,606; *Chem. Abstracts*, **38**, 5619 (1944).

[199] Alder and Rickert, U. S. Patents, 2,351,311 and 2,336,208; *Chem. Abstracts*, **38**, 5222, 2961 (1944).

[200] Bruson, U.S. Patent, 2,411,869 (1946); *Chem. Abstracts*, **41**, 1707 (1947).

[201] Bruson, U.S. Patent, 2,412,799 (1946); *Chem. Abstracts*, **41**, 1708 (1947).

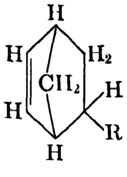
[202] Bruson, U.S. Patent, 2,417,000; *Chem. Abstracts*, **41**, 3819 (1947).

[203] Bergmann and Japhe, *J. Am. Chem. Soc.*, **69**, 1826 (1947).

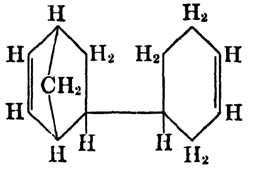
[204] Bruson and Riener, *J. Am. Chem. Soc.*, **68**, 8 (1946).

[205] Bartlett and Schneider, *J. Am. Chem. Soc.*, **68**, 6 (1946).

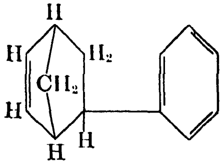
The most striking evidence of the great additive tendency of cyclopentadiene, lies in the fact that it also adds simple hydrocarbons such as propylene[31,206,207] and ethylene.[31,207] The former gives a small yield of adduct but the addition proceeds in a completely normal manner with the formation of methylbicyclo-[2.2.1]-heptene (CCXXXVIII) (R = CH_3). The latter produces bicyclo-[2.2.1]-heptene (CCXXXVIII) (R = H) in excellent yield.



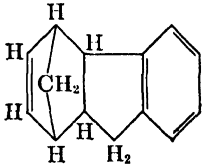
(CCXXXVIII)



(CCXXXIX)



(CCXL)



(CCXLI)

Addition products of cyclopentadiene with vinylcyclohexene (CCXXXIX),[208] styrene (CCXL),[208] and indene (CCXLI)[208] can also be prepared by heating the components. The last cases cited are, of course, not confined to cyclopentadiene. Analogous reactions can be accomplished with other dienes, though less smoothly.

The thermal polymerization of cyclopentadiene, which represents a series of diene syntheses, has already been referred to.

It is apparent from this survey that the great majority of all additions of cyclopentadiene to unsaturated systems, such as $>C{=}C<$, $-C{\equiv}C-$, and $-N{=}N-$, proceed with the formation of six-membered rings. To date only a single exception to this rule is known with certainty; namely,

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[206] Alder and Windemuth, unpublished observation.

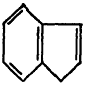
[207] Nudenberg and Butz, *J. Am. Chem. Soc.*, **66**, 307 (1944). Alder and Windemuth, *Ber.*, **71**, 1939 (1938) (foot-note).

[208] Alder and Rickert, *Ber.*, **71**, 373, 379 (1938).

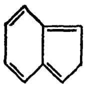
the addition of cyclopentadiene to ketene[209] and its derivatives.[210,211] In these cases the additions take place with the formation of four-membered rings (see page 401).

So far, only the parent substance, cyclopentadiene, itself has been considered. This component has also been varied extensively. In its place, alkyl- and aryl-substituted cyclopentadienes[212,213] as well as cyclopentadienecarboxylic acid[214] have been used. Without exception, these compounds add to the same degree and with the same ease to olefin and acetylene compounds as does the simple parent substance. Recently hexachlorocyclopentadiene has been added to maleic anhydride, benzoquinone acrylonitrile, and vinyl methyl ketone.[215]

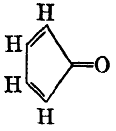
Indene (CCXLII), which has already been described as a dienophile (pp. 423, 451), also reacts as a diene with such compounds as maleic anhydride and ethyl acetylenedicarboxylate. In this reaction indene functions as a benzocyclopentadiene, a tautomeric form (CCXLIII) of the hydrocarbon.[216] The derivatives of cyclopentadienone (CCXLIV) and fulvene (CCXLV), on which an especially large amount of research has been done, should also be mentioned. Diene syntheses with these compounds will be discussed separately somewhat later, not because of any fundamental difference in the syntheses, but because of certain properties of the normally formed adducts.



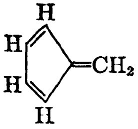
(CCXLII)



(CCXLIII)



(CCXLIV)



(CCXLV)

(*b*) *Synthesis of Norcamphor and Camphor Group.* By addition reactions similar to those described above a great variety of derivatives of the bicyclo-[2.2.1]-heptane ring system becomes accessible. One of the most significant contributions that the diene synthesis has made to preparative organic methods lies in this field. Compounds with this ring skeleton, such as the bicyclic terpenes and camphor types, are very widely distributed as natural products. Any convenient preparation from available

[209] Brooks and Wilbert, *J. Am. Chem. Soc.*, **63**, 870 (1941).

[210] Alder and Rickert, *Ann.*, **543**, 15 (1940) gives a compilation of the literature.

[211] Compare the reaction of ketene acetal with maleic anhydride (see p. 393).

[212] Alder and Holzrichter, *Ann.*, **524**, 145 (1936). Alder and Windemuth, *Ann.*, **543**, 28, 56 (1940). Drake and Adams, *J. Am. Chem. Soc.*, **61**, 1326 (1939).

[213] Rühmann, Dissertation, Bonn (1939).

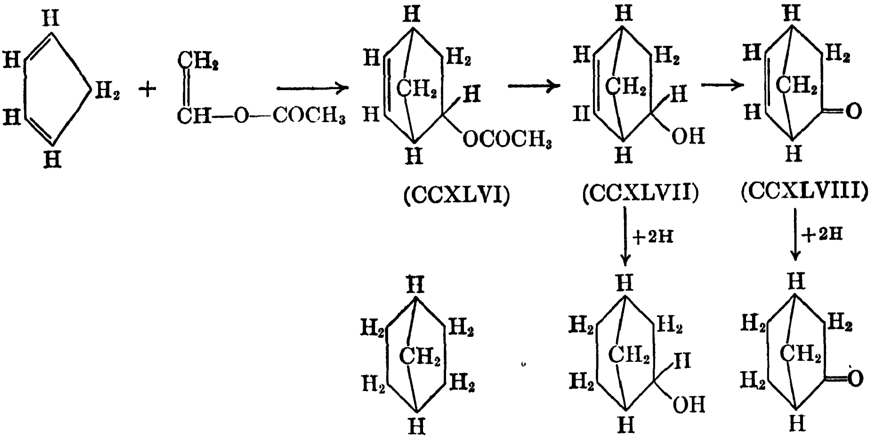
[214] Alder and Stein, *Ann.*, **514**, 12 (1934). Alder and Windemuth, *ibid.*, **543**, 56 (1940).

[215] Prill, *J. Am. Chem. Soc.*, **69**, 62 (1947).

[216] Alder, Pascher, and Vagt, *Ber.*, **75 B**, 1501 (1942).

materials, therefore, possesses considerable interest. These compounds have been made by ingenious application of the traditional methods of organic syntheses, but such preparations are not satisfactory from the standpoint of preparative organic chemistry. This was reserved for the diene synthesis, the efficiency of which will be illustrated in a single example.

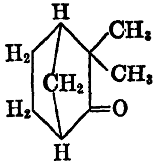
Vinyl acetate and cyclopentadiene, two materials available in technical quantities, react smoothly when heated to yield the acetate (CCXLVI) of a bicyclic alcohol (CCXLVII). Oxidation of the alcohol produces dehydronorcamphor (CCXLVIII), while hydrogenation leads to norborneol (CCXLIX). Reduction of the ketone (CCXLVIII) gives norcamphor (CCL).[85,217]



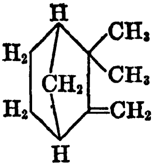
(CCXLVI) (CCXLVII) (CCXLVIII)

(CCLI) (CCXLIX) (CCL)

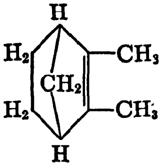
Reduction of norcamphor by the Wolff-Kishner method gives the parent hydrocarbon of the whole series, norbornylane (CCLI). From norcamphor, camphenilone (CCLII), camphene (CCLIII), and the santene of sandalwood oil (CCLIV) can be obtained by known reactions.[218]



(CCLII)



(CCLIII)



(CCLIV)

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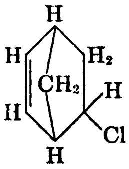
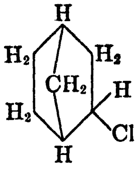
[217] Compare also the older methods (Diels and Alder, *Ann.*, **470,** 62 (1929); Kommpa and Beckmann, *Sucmalaisen Tiedeakatemian Toimituksia, Ann. Acad. Sci. fennicae, Series A*, 39, 7 (1934); *Ann.*, 512, 172 (1934)).

[218] Diels and Alder, *Ann.*, **486,** 202 (1931).

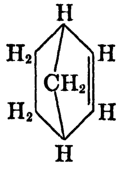
The versatility of the diene synthesis in this field is not completely apparent from the above data. Its full significance for the synthesis of bicyclic systems of this type lies in the fact that the basic reaction is of general application. If the vinyl acetate used in the above example is replaced by halogenated ethylene, halogenated norbornylene and norbornylane can be obtained. These in turn can be converted to numerous other derivatives. Dehydronorbornyl chloride (CCLV)—easily prepared from vinyl chloride and cyclopentadiene—can be hydrogenated to norbornyl



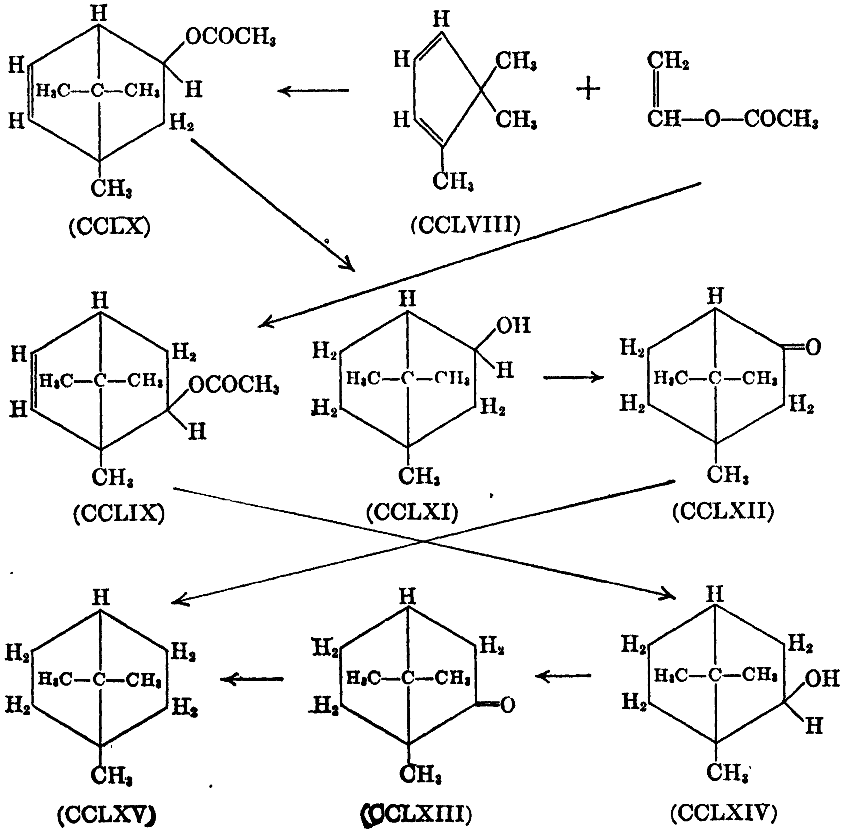
(CCLV)



(CCLVI)



(CCLVII)



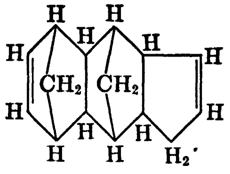
(CCLX) (CCLVIII) (CCLIX) (CCLXI) (CCLXII) (CCLXV) (CCLXIII) (CCLXIV) chloride (CCLVI), which changes to norbornylene (CCLVII) by cleavage of HCl.[85]

In general, this brief résumé shows clearly that the diene synthesis has opened up the whole field of simple bicyclo-[2.2.1]-heptane compounds for preparative work. In addition to the possibilities pointed out above variations in the diene component should also be considered. However, only one example will be mentioned; namely, the addition of 1,5,5-trimethyl-1,3-cyclopentadiene (CCLVIII) to vinyl acetate. This synthesis, which proceeds as indicated in the reactions on page 454, leads to camphane (CCLXV).

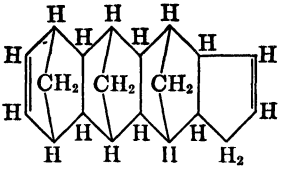
Borneol (CCLXIV), epiborneol (CCLXI), camphor (CCLXIII), and epicamphor (CCLXII) are formed as intermediates.[219]

This simple synthesis of a naturally occurring, methylated bicyclo-[2.2.1]-heptane is a particularly significant indication of the serviceability of the method. This special case embodies all other conceivable varieties of this type. The problem of their preparation depends primarily upon the synthesis of suitable starting materials, especially suitable derivatives of cyclopentadiene.

(c) *Condensed Ring Systems with Bridges.* In addition to the simple types of compounds considered above, cyclopentadiene can undergo a diene synthesis with itself, to form condensed bicyclo-[2.2.1]-heptane rings. Such combinations are the result of the thermal polymerization of cyclopentadiene, and lead, in the early stages of the phenomenon, to tri- and tetracyclopentadienes (CCLXVI and CCLXVII):

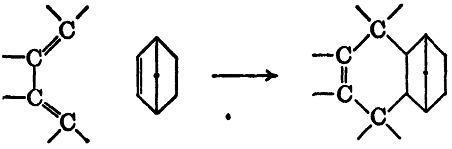


(CCLXVI)



(CCLXVII)

It should be pointed out that the formation of these polymers of cyclopentadiene is only a special case of the general reaction, and depends upon the fact that the double bond in the bicyclo-[2.2.1]-heptene system has the ability to add dienes.[220]



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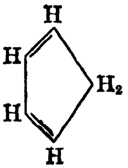
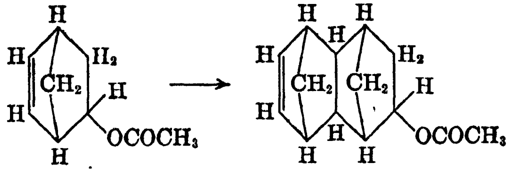
[219] Alder and Windemuth, *Ann.*, 543, 41 (1940).
[220] Alder and Stein, *Ann.*, 496, 204 (1932).

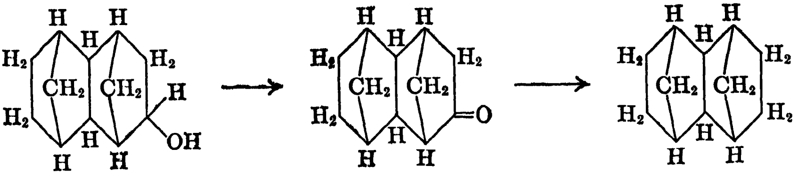
From this information a general method has been evolved for the synthesis of condensed polycyclic bridged ring compounds. The synthesis of the tetracyclic 1,4,5,8-bisendomethylenedecalin type illustrates the reaction. When cyclopentadiene is added to vinyl acetate, the simple adduct, norbornylene-ol acetate (CCXLVI), is obtained only when excess of vinyl acetate is used. In this reaction the compound (CCLXVIII) formed from 2 moles of cyclopentadiene and 1 of vinyl acetate is obtained as a by-product. By changing the proportion of the reactants and by the use of higher temperatures, the compound (CCLXVIII) becomes the main product.[85]





(CCXLVI) (CCLXVIII)

Hydrogenation of CCLXVIII, followed by saponification, gives 1,4,5,8-bisendomethylene-β-decalol (CCLXIX) from which the ketone (CCLXX) can be obtained. From the latter, the parent hydrocarbon of a hitherto unknown class of compounds, 1,4,5,8-bisendomethylenedecalin (CCLXXI),[221] can be secured in the usual manner.



(CCLXIX) (CCLXX) (CCLXXI)

Further generalization of this type of reaction (substitution of vinyl acetate by other olefins and use of other dienes in place of cyclopentadiene) is obvious.[222]

(*d*) *Transition into Bicyclo-[3.2.1]-octane Series.* The series of compounds represented by bicyclo-[3.2.1]-octane (CCLXXIV) is another class of bicyclic bridged ring compounds that has become available through the diene synthesis with cyclopentadiene. Compounds of this group are obtained from the addition product of cyclopentadiene and allylamine. Treatment of the hydrogenated adduct (CCLXXII) with nitrous acid

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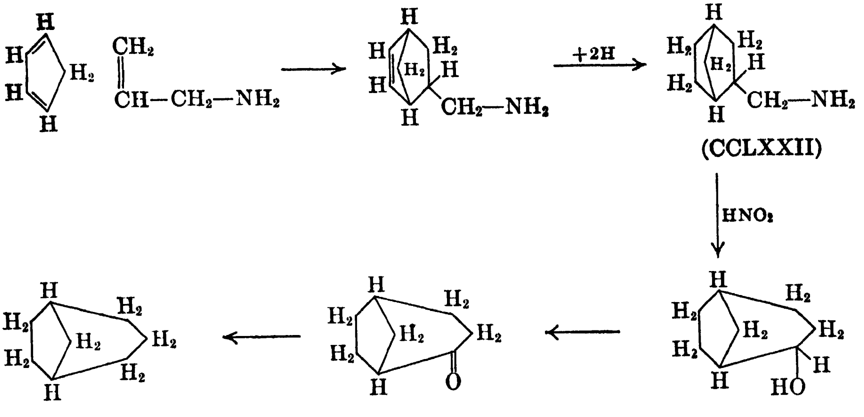
[221] Alder and Windemuth, *Ber.*, 71, 2409 (1938).

[222] For the synthesis of other condensed systems with bridges, see Alder and Rickert, *Ber.*, 71, 373, 379 (1938).



(CCLXXII)

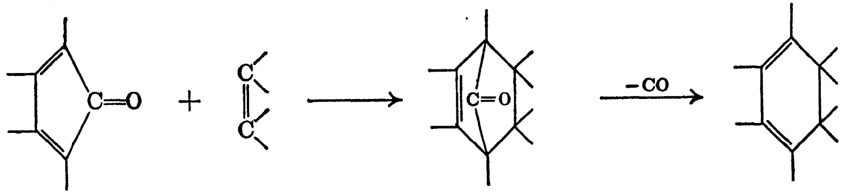
(CCLXXIV)

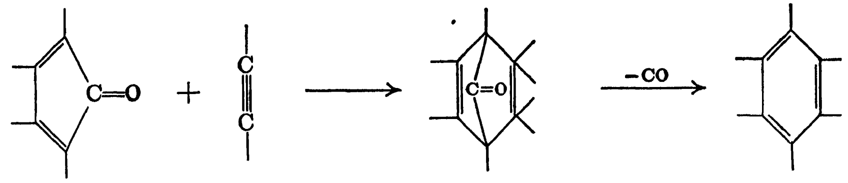
(CCLXXIII)

results in the formation of an enlarged ring, an alcohol of the bicyclo-[3.2.1]-octane series (CCLXXIII).[223]

This class of bicyclic bridged ring compounds was previously represented by very few substances, which could only be obtained with great difficulty. The groundwork for their methodical study has been indicated in the procedures described above.

(*e*) *Cyclopentadienone Type as Diene Components.* Application of the diene synthesis to derivatives of cyclopentadienone results in compounds that suggest new preparative procedures. This depends upon the fact that the primary adduct formed by a normal reaction loses its carbonyl bridge when heated. Derivatives of benzene or dihydrobenzene are formed when olefinic and acetylenic dienophiles, respectively, are used in the synthesis:





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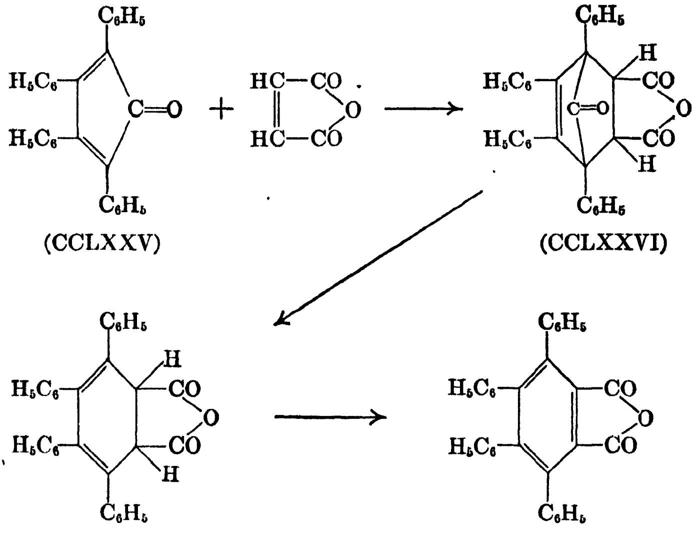
[223] Alder and Windemuth, *Ber.*, 71, 2404 (1938).

In the case of the olefin component it is not unusual for a dehydrogenation to follow the cleavage of carbon monoxide to give a compound of the aromatic type. The following case[224] illustrates the reaction: tetraphenylcyclopentadienone (CCLXXV) (tetracyclone) and maleic anhydride react in boiling benzene to give the normal adduct 3,6-endocarbonyl-3,4,5,6-tetraphenyl-1,2,3,6-tetra-hydrophthalic anhydride (CCLXXVI) in almost quantitative yield:



(CCLXXV) (CCLXXVI)

(CCLXXVII) (CCLXXVIII)

If the primary adduct (CCLXXVI) is heated in chlorobenzene, carbon monoxide is split out and 3,4,5,6-tetraphenyldihydrophthalic anhydride (CCLXXVII) is formed. The latter compound is obtained directly if the addition of the components is carried out in boiling chlorobenzene.

Finally, if the reaction is carried out in boiling nitrobenzene, the solvent acts as a dehydrogenating agent and tetraphenylphthalic anhydride (CCLXXVIII) results. However, the three compounds, CCLXXV, CCLXXVII, and CCLXXVIII, can be obtained from tetraphenylcyclopentadienone and maleic anhydride by the use of solvents other than those specified.

In general the primary products formed with acetylene derivatives are not stable, and benzene derivatives are obtained directly. Tetraphenylcyclopentadienone and phenylpropiolic acid give pentaphenylbenzoic acid (CCLXXIX).[225]

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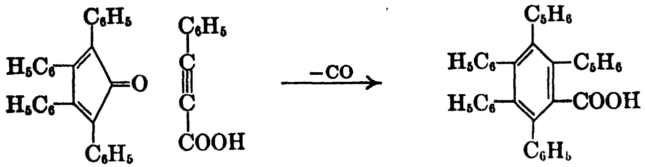
[224] Dilthey *et al.*, *Ber.*, 66, 1627 (1933); 67, 1959 (1934).

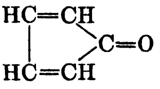
[225] For the synthesis of pentaphenylbenzaldehyde see p. 419.



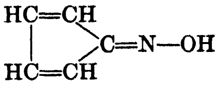
(CCLXXIX)

This reaction has acquired considerable significance for the synthesis of highly arylated types of compounds.[226] Its value will become evident from the reactions considered below.

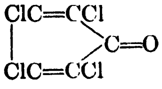
The simplest ketone of the cyclopentadiene series, cyclopentadienone (*a*), is unknown. Its oxime, isonitrosocyclopentadiene (*b*),[227] and its perchloro derivative, tetrachlorocyclopentadienone (*c*),[228] are known only in the dimeric forms (*e* and *f*):



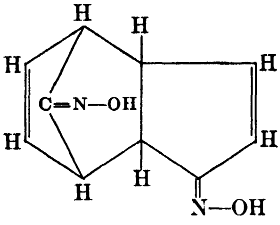
(*a*)



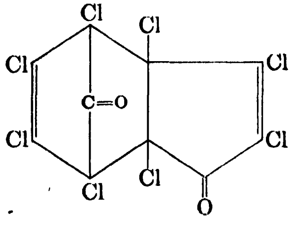
(*b*)



(*c*)



(*e*)



(*f*)

These compounds have been of little use in preparative work. This is not the case with the more highly substituted types following: 3,4-diphenylcyclopentadienone,[229] 2,3,4-triphenylcyclopentadienone,[230] 2,3,5-triphenylcyclopentadienone,[230] 2,3,4,5-tetraphenylcyclopentadienone (tetracyclone),[231] 2-methyl-3,4-diphenylcyclopentadienone,[232] 2,5-dimethyl-3,4-

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[226] Dilthey *et al.*, *Ber.*, **66**, 1627 (1933); **67**, 495, 1959, 2004 (1934); **68**, 1159 (1935); **71**, 974 (1938); **73**, 430 (1940); *J. prakt. Chem.*, **151**, 185, 257 (1938); **153** 35 (1939); **154**, 238 (1940); **156**, 27 (1940). Allen and Sheps, *Can. J. Research*, **11**, 171 (1934). Arbuzov, Abramov, and Dewaztov, *J. Gen. Chem.* (*U. S. S. R.*), **9**, 1559 (1939); *Chem. Zentr.*, **1940,I**, 705; *Chem. Abstracts*, **34**, 2839 (1940). Allen *et al.*, *J. Am. Chem. Soc.*, **61**, 521 (1939); **62**, 656 (1940).

[227] Thiele, *Ber.*, **33**, 669 (1900). Alder and Stein, *Ann.*, **496**, 205 (1932).

[228] Zincke, *Ber.*, **26**, 515 (1893); *Ann.*, **367**, 1 (1909); **394**, 3 (1912).

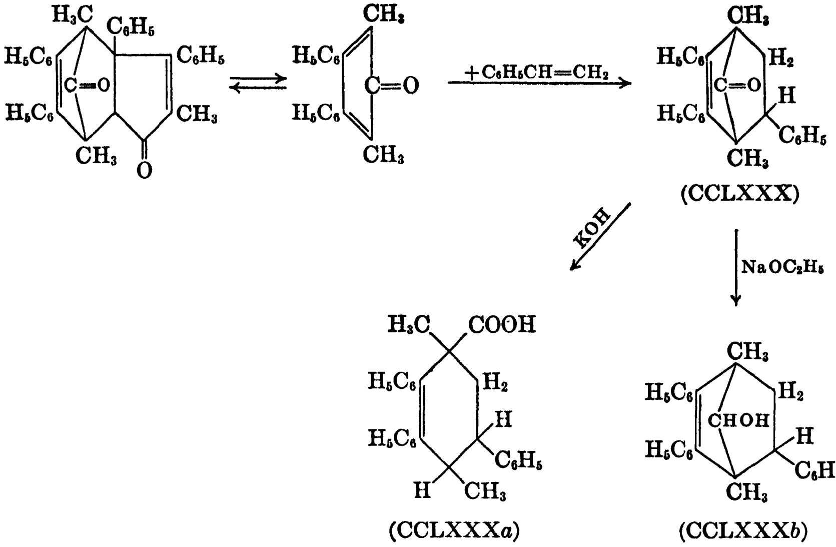
[229] Allen and Spanagel, *Can. J. Research*, **8**, 414 (1933); *J. Am. Chem. Soc.*, **54**, 4338 (1932); **56**, 3773 (1933). Allen and Gates, *J. Am. Chem. Soc.*, **64**, 2123 (1942).

[230] Dilthey and Schommer, *J. prakt. Chem.*, **136**, 293 (1933).

[231] Dilthey and Quint, *J. prakt. Chem.*, **128**, 139 (1930).

[232] Allen and VanAllan, *J. Am. Chem. Soc.*, **64**, 1260 (1942).

diphenylcyclopentadienone.[233] Of these, only 2,3,4,5-tetraphenylcyclopentadienone exists in the monomeric form and does not dimerize even under extreme conditions of temperature. All the other compounds listed above exist only in the dimeric form. Dimeric 2,5-dimethyl-3,4-diphenylcyclopentadienone dissociates easily in solution. The monomer thus formed reacts readily even with inactive dienophiles. Styrene, for example, gives the endocarbonyl compound (CCLXXX):



(CCLXXX)

(CCLXXXa)

(CCLXXXb)

This substance is cleaved by alcoholic potassium hydroxide to give the acid (CCLXXX*a*),[232] or reduced to give an alcohol (CCLXXX*b*) of the bicyclo-[2.2.1]-heptene system.[234]

Dimeric 2-methyl-3,4-diphenylcyclopentadienone (CCLXXXI) also dissociates but only under more drastic conditions. Thus, it reacts with maleic anhydride at 200°C. to give two products, (CCLXXXII) and (CCLXXXIII). The former is derived from the monomeric form, while the latter results from the addition of maleic anhydride to the dienone (CCLXXXIV) formed by decarbonylation of the dimer.[235]

The 2,3,4- and 2,3,5-triphenyl compounds are also dimeric. The latter dissociates, for on treatment with phenylacetylene, 1,2,4,5-tetraphenylbenzene is obtained.[236] The former has been reported[237] but no reactions

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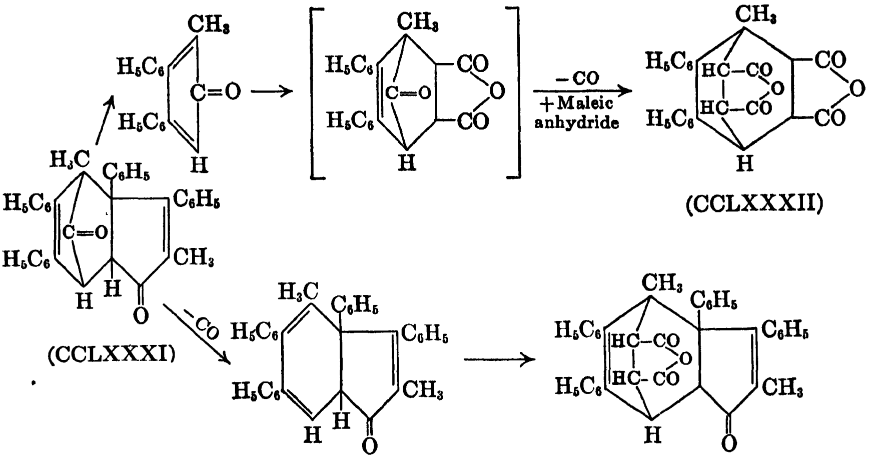
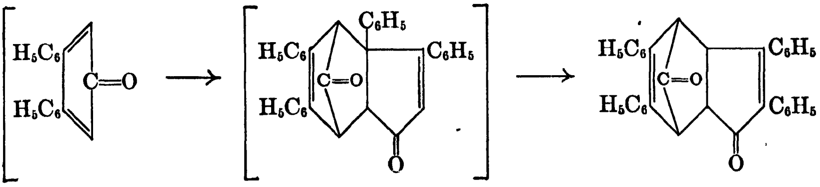
[233] Allen, Jones, and VanAllan, *J. Am. Chem. Soc.*, **68**, 708 (1946).
[234] Allen, Jones, and VanAllan, *J. Org. Chem.*, **11**, 268 (1946).
[235] Allen and VanAllan, *J. Org. Chem.*, **10**, 333 (1945).
[236] Dilthey and Hurtig, *Ber.*, **67**, 2004 (1934).
[237] Geissman and Koelsch, *J. Org. Chem.*, **3**, 502 (1938). Arbuzov, *J. Gen. Chem.* (*U. S. S. R.*), **12**, 211 (1942); *Chem. Abstracts*, **37**, 2732 (1943).



(CCLXXXI) (CCLXXXII) (CCLXXXIV) (CCLXXXIII)

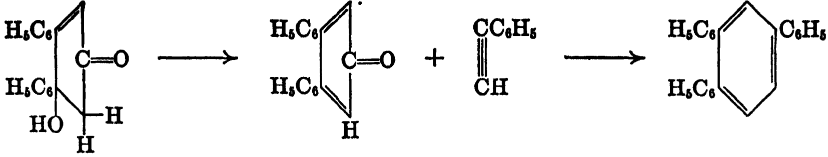
with it have been indicated, though derivatives of it have been obtained from the corresponding anhydroacetonebenzil.[236]

On the other hand, 3,4-diphenylcyclopentadienone, though it exists as a dimer, is not dissociated in solution. The structure of the dimer is shown by CCLXXXV. In its formation there has been a 1,3 shift of a phenyl group.[229] This effectively prevents reversal of the reaction.

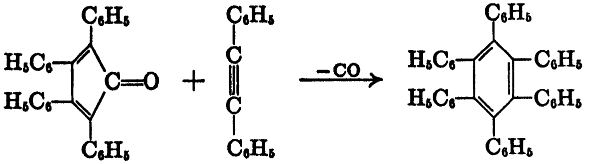


(CCLXXXV)

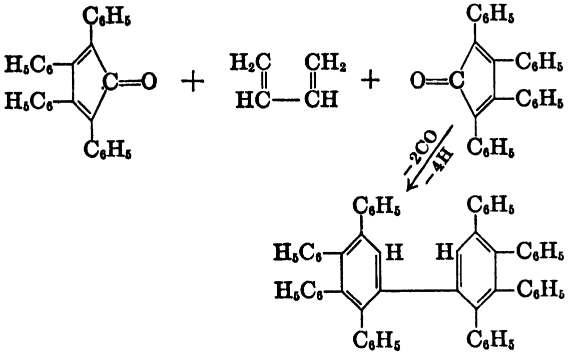
However, since the dimerization of these cyclopentadienones follows the formation of the monomer from the corresponding anhydroacetonebenzil, it is possible for dienophiles to react with the monomer the moment it is formed. This method has been used to advantage in the synthesis of certain highly substituted derivatives of the toluene series.[235] Thus, phenylacetylene acts with 2-methyl-3,4-diphenylcyclopentadienone as it is formed from the corresponding anhydroacetonebenzil to give 2,3,6-triphenyltoluene, thus:



Tetracyclone has been shown to be a very serviceable component for the diene synthesis, since it reacts with numerous olefins and acetylenes to form highly arylated compounds. The synthesis of tetraphenylphthalic anhydride (CCLXXVIII) and pentaphenylbenzoic acid (CCLXXIX) have already been described. The preparation of the hitherto unknown hydrocarbons, hexaphenylbenzene (CCLXXXVI) and octaphenylbiphenyl (CCLXXXVII), from tetracyclone by the use of tolane[236] and butadiene,[238] respectively, may be cited as further characteristic examples which are chosen from a large group[236]:

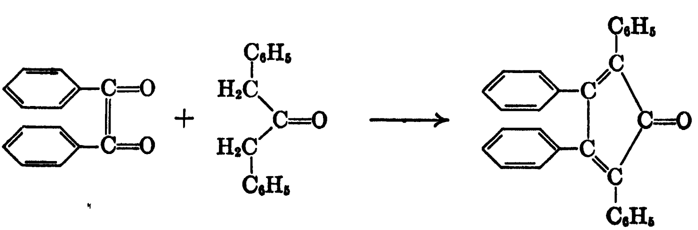


(CCLXXXVI)



(CCLXXXVII)

An especially important consideration, which bestows increased significance to the method, lies in the fact that the procedure for the preparation of tetracyclone is a general one. The unsaturated ketone is prepared by the condensation of dibenzyl ketone with benzil.[231]



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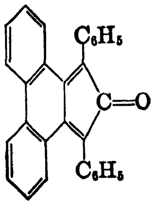
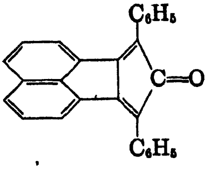
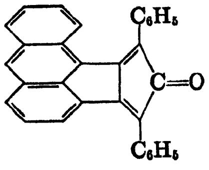
[238] Dilthey *et al.*, *Ber.*, 68, 1159 (1935).

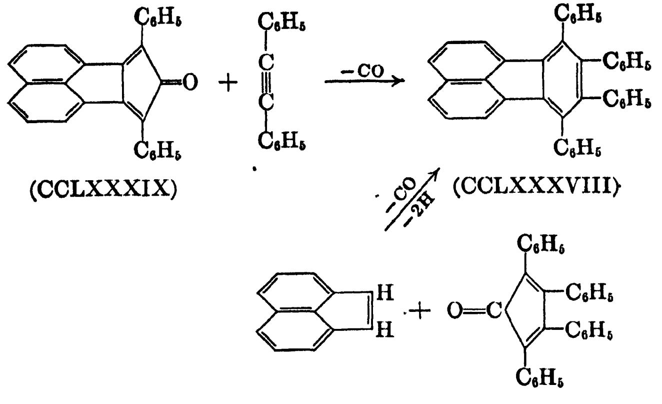
Other 1,2-diketones, such as phenanthrenequinone, acenaphthenequinone, and aceanthraquinone can be used instead of benzil, and new derivatives of cyclopentadienone are obtained[239]:







Phencyclone and *acecyclone*, particularly, have proved useful as starting materials for the synthesis of new highly arylated compounds.[240] The reactions correspond so closely with those described for tetracyclone that their description can be confined to the following examples in which a certain amount of overlapping is evident. The hydrocarbon (CCLXXXVIII) can be prepared from acecyclone (CCLXXXIX) and tolane, as well as from tetracyclone (CCLXXV) and acenaphthalene (CCXC) by the diene synthesis.[241] In the second case a dehydrogenation as well as a cleavage of carbon monoxide is effected:



(CCLXXXIX) (CCLXXXVIII)

(CCXC) (CCLXXV)

The use of compounds like tolane and acenaphthalene as components indicates the great versatility of the reaction. This is also apparent in numerous other observations in this group of the diene synthesis. In addition to known types like maleic anhydride, phenylpropiolic acid, and phenylpropiolaldehyde, less active dienophiles have been used directly with success; *e.g.*, cyclohexene, acetylene, butadiene with both double bonds, and the —C≡N group in benzonitrile. Indeed, observations have been noted that permit the conclusion that substituted cyclopentadienones also add to a molecule of oxygen,[242] O═O, and to the O═N— group of nitroso compounds[243] in the manner of the diene synthesis. In the course of this discussion these latest results can only be mentioned. They indicate that further development in the cyclopentadienone group promises to become especially informative.

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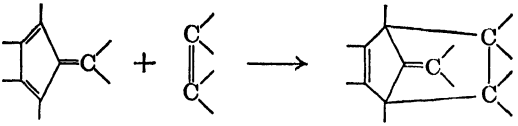
[239] Dilthey, ter Horst, and Schommer, *J. prakt. Chem.*, **143**, 189 (1935).

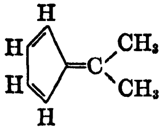
[240] Dilthey *et al.*, *J. prakt. Chem.*, **148**, 53 (1937); *Ber.*, **71**, 974 (1938); **73**, 430 (1940). Arbuzov *et al.*, *J. Gen. Chem.* (*U. S. S. R.*), **9**, 1559 (1939); *Chem. Zentr.*, 1940,I, 705; *Chem. Abstracts*, **34**, 2839 (1940). See also Abramov and Tsyplenkova, *Bull, Akad. Sci. U. R. S. S., Classe sci. chim.*, 1944, 60; *Chem. Abstracts*, **39**, 1639 (1945); Arbuzov and Akhmed-Zade, *J. Gen Chem.* (*U. S. S. R.*), **12**, 212 (1942); *Chem. Abstracts*, **37**, 2733 (1943).

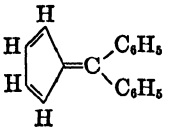
[241] Dilthey, Henkels, and Schäfer, *Ber.*, **71**, 974 (1938).

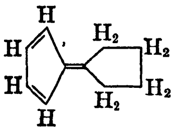
(*f*) *Fulvene and Fulvenecarboxylic Acids.* Diene syntheses with fulvene, which has a system of three crossed double bonds in conjugated position, result in adducts which also belong to the bicyclo-[2.2.1]-heptane series. It has been shown that addition reactions involve the cyclic double bonds, while the semicyclic bond remains intact. Consequently a hitherto unknown type of bicyclo-[2.2.1]-heptane derivative with an unsaturated bridge results[213,244]:

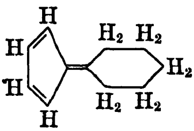


Little attention has been given to the synthesis of this group of compounds. Only the reactions of dimethyl- (CCXCI), diphenyl- (CCXCII), tetramethylene- (CCXCIII), and pentamethylenefulvene (CCXCIV) with maleic anhydride and dimethyl acetylene dicarboxylate have been thoroughly studied:


(CCXCI)


(CCXCII)


(CCXCIII)


(CCXCIV)

The reaction proceeds with great ease in all cases, even at room temperature and in dilute solution; *e.g.*,

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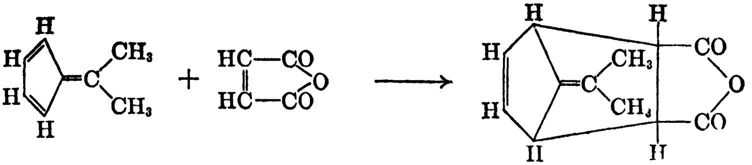
[242] Dilthey *et.al.*, *J. prakt. Chem.*, **151**, 97 (1938).

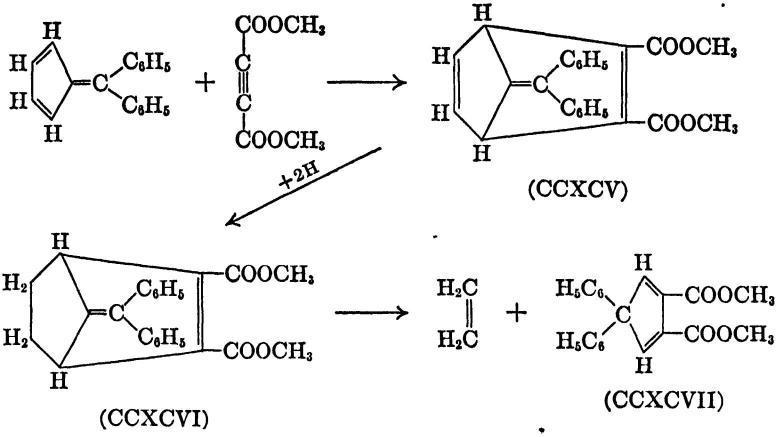
[243] Dilthey *et al.*, *J. prakt. Chem.*, **153**, 35 (1939); **156**, 27 (1940).

[244] Diels and Alder, *Ber.*, **62**, 2086 (1929). Kohler and Kable, *J. Am. Chem. Soc.*, **57**, 917 (1935).



The adducts with maleic anhydride are characterized by the fact that they are dissociated with remarkable ease into their components. By hydrogenation of the double bond stabilization is effected.

A degradation of the addition products of various fulvenes with methyl acetylenedicarboxylate, which is of preparative interest, has been observed.[245] It is illustrated by the adduct (CCXCV) from diphenylfulvene and methyl acetylenedicarboxylate. The catalytic hydrogenation of this three-fold unsaturated ester (CCXCV) can be carried out in such a way that only the cyclic double bond is saturated. The resulting dihydro compound (CCXCVI) undergoes a very smooth thermal dissociation into ethylene and methyl diphenylfulvenedicarboxylate (CCXCVII). Thus, a new class of fulvenecarboxylic acids becomes accessible.



(CCXCV)

(CCXCVI)

(CCXCVII)

(2) Bicyclo-[2.2.2]-octane Series. The bicyclo-[2.2.2]-octane type of product results when the diene synthesis is applied to compounds in which the conjugated double bonds are contained in a six-membered ring. Before the discovery of the diene synthesis representatives of this class of bicyclic bridged compounds were unknown. As ring homologues of the camphor series, they are characterized by a complete lack of strain; their preparation, on this basis alone, would have been of some importance to the knowledge of bridged compounds.

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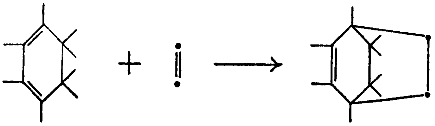
[245] Alder and Trimborn, unpublished observation.

The diene synthesis has successfully bridged this gap in the systematization of alicyclic compounds. In addition it has produced an abundance of important advancements in this field and has been responsible for the development of many significant practical applications.

The great variety of compounds that has been obtained in this field will be discussed by groups as follows: (*a*) 1,3-cyclohexadiene and its simple homologues as components in the diene synthesis, (*b*) the synthesis of cantharidin and cantharic acid, (*c*) the addition of 1,3-cyclohexadiene to acetylene derivatives, (*d*) resin acids and monocyclic terpenes and their significance in the production of lacquers and artificial resins, (*e*) ergosterol and its irradiation products, (*f*) the anthracene type, and (*g*) thebaine and dihydropyridine.

(*a*) *Cyclohexadiene and Its Homologues as Components.* Many dienophiles have been added to 1,3-cyclohexadiene. It can be shown that in almost all cases the additions proceed normally, and lead to compounds of the bicyclo-[2.2.2]-octane series:



α,β-Unsaturated carbonyl compounds like acrolein,[246] maleic anhydride,[247] dibromomaleic anhydride,[248] *p*-quinone,[90] α-naphthoquinone,[90] and methyl acetylenedicarboxylate,[249] as well as less active types like 1,3-cyclohexadiene[250] itself and vinyl acetate,[251] have been used as olefin components in such additions. In general the additions proceed more slowly than the corresponding reactions with cyclopentadiene. However, many of the reactions with 1,3-cyclohexadiene give quantitative yields when carried out in dilute solution at room temperature. In other cases moderate heating is necessary. Temperatures above 160°C. should be avoided, especially for investigations in the liquid phase, for 1,3-cyclohexadiene dimerizes under these conditions. It differs from cyclopentadiene in this respect, for the latter is quite stable under the same conditions. The dimerization follows an analogous course and yields a bicyclo-[2.2.2]-octane derivative.[250]

Diene syntheses with 1,3-cyclohexadiene and dienophiles that react slowly are not improved by the use of elevated temperatures. Under these conditions, the 1,3-cyclohexadiene is removed by the formation of a stable dimer (CCXCVIII):

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[246] Diels and Alder, *Ann.*, 478, 144 (1930).

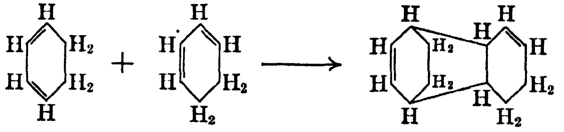
[247] Diels and Alder, *Ann.*, 460, 115 (1928); Daudel and Pullman, *Compt. rend.*, 222, 86 (1946).

[248] Diels and Alder, *Ann.*, 478, 147 (1930).

[249] Diels and Alder, *Ann.*, 490, 241 (1931).

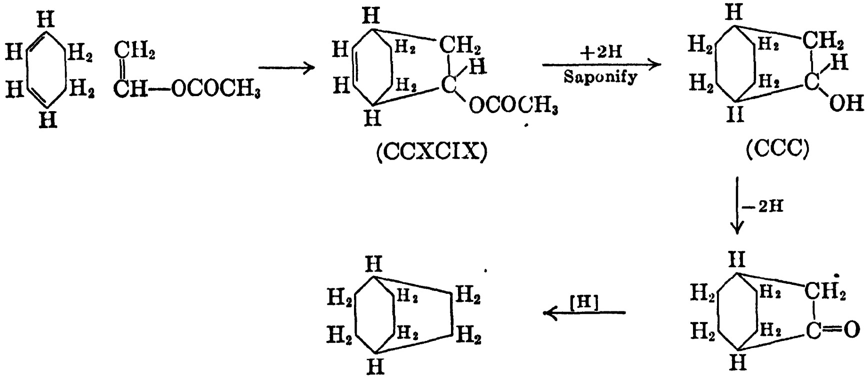
[250] Alder and Stein, *Ann.*, 496, 197 (1932).

[251] Alder and Rickert, *Ann.*, 543, 23 (1940).



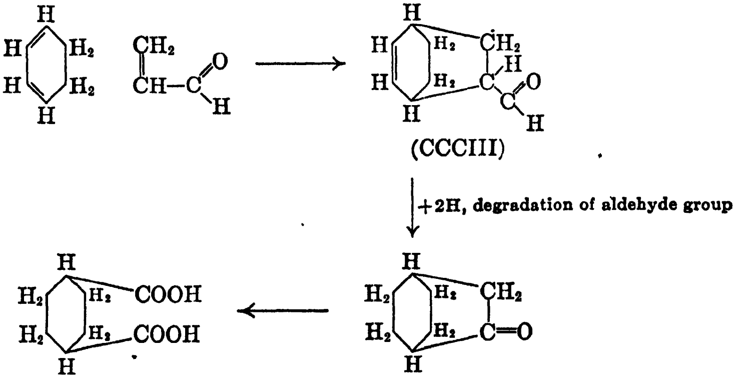
(CCXCVIII)

Thus, the diene can be added to vinyl acetate but only a moderate yield of the adduct (CCXCIX) is obtained. Hydrogenation and saponification of the adduct give bicyclo-[2.2.2]-octanol (CCC)[251]:



(CCXCIX) (CCC) (CCCII) (CCCI)

Oxidation of the alcohol (CCC) gives bicyclo-[2.2.2]-octanone (CCCI) and reduction of this by the Wolff-Kishner method yields bicyclo-[2.2.2]-octane (CCCII), the parent hydrocarbon of the whole series.[252]

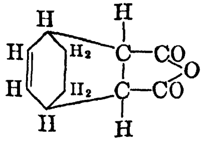


(CCCIII) (CCCIV) (CCCI)

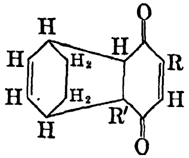
The ketone (CCCI) can be obtained in another way. Acrolein adds to 1,3-cyclohexadiene to give a bicyclic unsaturated aldehyde (CCCIII).[194] The addition of this α,β-unsaturated aldehyde to the diene hydrocarbon proceeds more easily than vinyl acetate, but this is of no advantage for the synthesis of the ketone (CCCI), because the subsequent degradation of the aldehyde group (by oxidation of the enol acetate) is not a very smooth reaction.

The conversion of bicyclo-[2.2.2]-octanone (CCCI) to *cis*-hexahydroterephthalic acid (CCCIV)[246] shows that acrolein and vinyl acetate undergo 1,4 addition with 1,3-cyclohexadiene. Furthermore, a similar proof of structure applies to other adducts of 1,3-cyclohexadiene.

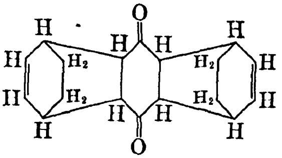
The addition of 1,3-cyclohexadiene to acrylic acid and maleic anhydride as well as to quinone and its derivatives takes place very easily, and yields carboxylic acids and quinones of the bicyclo-[2.2.2]-octane series. The anhydride (CCCV) is formed quantitatively when maleic anhydride and 1,3-cyclohexadiene are mixed together in benzene solution at room temperature.[247] The quinone (CCCVI) (R = R′ = H) is also obtained in quantitative yield from molecular amounts of *p*-quinone and 1,3-cyclohexadiene under the same conditions with alcohol as the solvent. The use of an excess of diene at a temperature of 100°C. gives biscyclohexadienequinone (CCCVII)[90,253]:



(CCCV)



(CCCVI)



(CCCVII)

When 1,3-cyclohexadiene reacts with 2-methyl-5-acetoxy-1,4-quinone in molecular proportions, addition occurs at both the acetoxyethene and the methylethene links. The principal product is that in which the acetate group is in the angular position, (CCCVI) (R = CH_3; R′ = $OCOCH_3$), but some of the other isomer (CCCVI) (R = $OCOCH_3$; R′ = CH_3) is also obtained.[254] The acetoxy compound loses acetic acid and ethylene at 200°C. to give 2-methyl-1,4-naphthoquinone.

The diene component has also been varied considerably. The complicated 1,3-cyclohexadiene derivatives of the terpene, resin acid, sterol, and thebaine series will be considered on page 473 ff. At this point several

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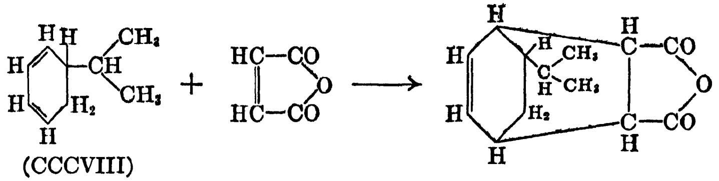
[252] Alder and Stein, *Ann.*, **514**, 18 (1934).

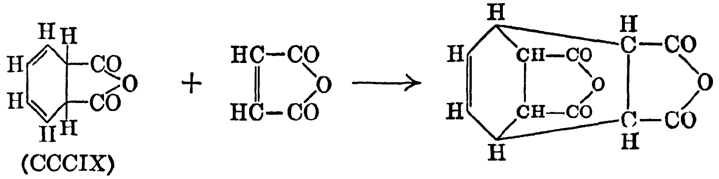
[253] Concerning the steric course of this addition see Alder and Stein, *Ann.*, **501**, 247 (1933); **514**, 1 (1934).

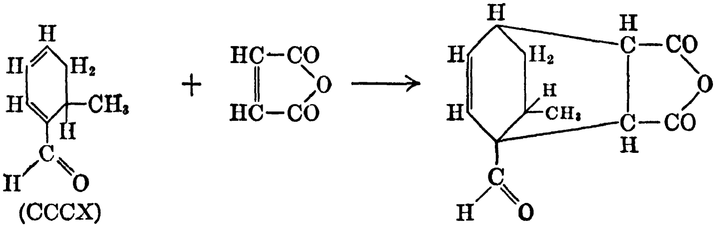
[254] Butz and Butz, *J. Org. Chem.*, **7**, 199 (1942).

derivatives of 1,3-cyclohexadiene, which show the wide scope of the diene synthesis in this group too, may be mentioned.

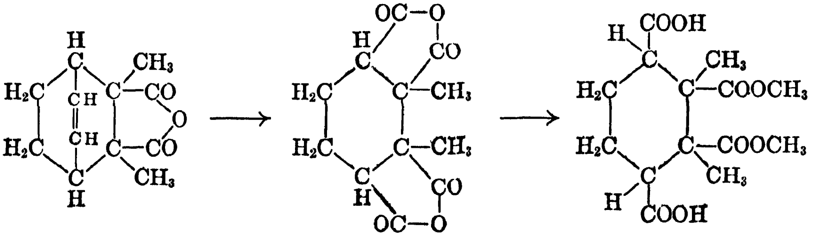
1-Isopropyl-2,4-cyclohexadiene (CCCVIII),[255] 1,2-dihydrophthalic anhydride (CCCIX),[256] and dihydro-*o*-tolualdehyde (CCCX)[257] add maleic anhydride with ease to form derivatives of bicyclo-[2.2.2]-octane.[258]


(CCCVIII)


(CCCIX)


(CCCX)

(*b*) *Cantharidin and Cantharic Acid.* The adduct (CCCXI) of 1,3-cyclohexadiene with pyrocinchonic anhydride has acquired some significance recently as the starting material for a synthesis of cantharidin


(CCCXI) (CCCXII) (CCCXIII)

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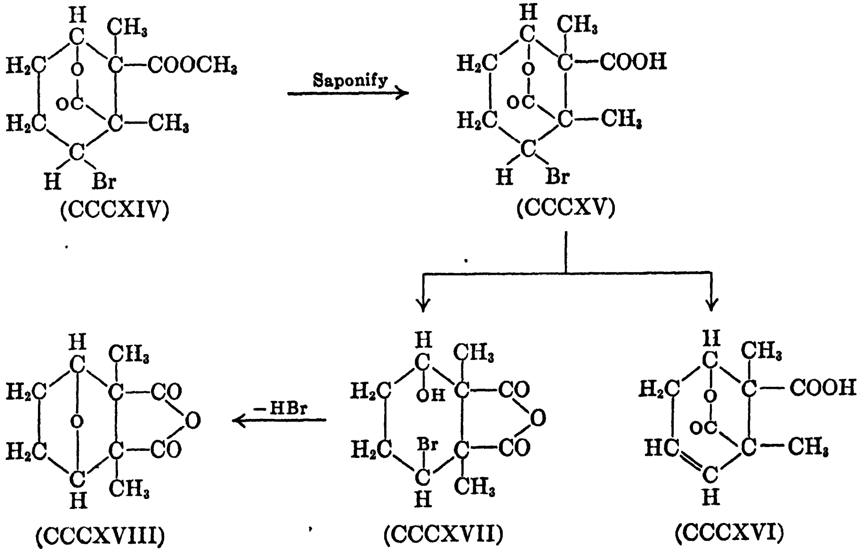
[255] Gillespie, Killen Macbeth, and Swanson, *J. Chem. Soc.*, 1938, 1820.

[256] Diels and Alder, *Ann.*, 490, 266 (1931).

[257] Grundmann and Löw, *Z. physiol. Chem.*, 256, 141 (1938). The statement of Allen, Ball, and Young, *Can. J. Research*, 9, 169 (1933), that dihydro-*p*-tolualdehyde does not react with maleic acid and α-naphthoquinone requires rechecking.

[258] For other cases of the same type, see Hultzsch, *Ber.*, 72, 1173 (1939); Schmitt, *Ann.*, 547, 258 (1941); compare also the additions of cyclic terpenes.

(CCCXVIII), which is carried out as follows[259]: An oxidative degradation of the adduct yields a double anhydride (CCCXII) of a tetracarboxylic acid, which can be converted easily into a dimethyl ester (CCCXIII). The free carboxyl groups are eliminated and replaced with bromine by the reaction of this halogen with the silver salt of the ester. The simultaneous cleavage of methyl bromide gives the methyl ester (CCCXIV) of a bromolactone acid (CCCXV). By melting the bromolactone acid (CCCXV) a remarkable pyrolysis is effected. It produces a mixture of cantharic acid (CCCXVI) and cantharidin (CCCXVIII), in which the unsaturated acid predominates. Cantharidin is probably formed from the intermediate bromohydroxyanhydride (CCCXVII).



The possibility of a direct synthesis of cantharidin from furan will be considered later (see page 498).

(*c*) *Cyclohexadiene Derivatives and Esters of Acetylenedicarboxylic Acid; Thermal Decomposition of Adducts and Formation of Benzene Derivatives.* The esters of acetylenedicarboxylic acid react in a normal manner with 1,3-cyclohexadiene and its derivatives to produce compounds of the bicyclo-[2.2.2]-octadiene type. Methyl acetylenedicarboxylate, for example, reacts smoothly with 1,3-cyclohexadiene to give methyl 3,6-endoethylene-3,6-dihydrophthalate (CCCXIX),[191] which can be converted to methyl 3,6-endoethylene-3,4,5,6-tetrahydrophthalate (CCCXX) by partial catalytic hydrogenation, and to methyl 3,6-endoethylene hexahydrophthalate (CCCXXI) by total reduction:

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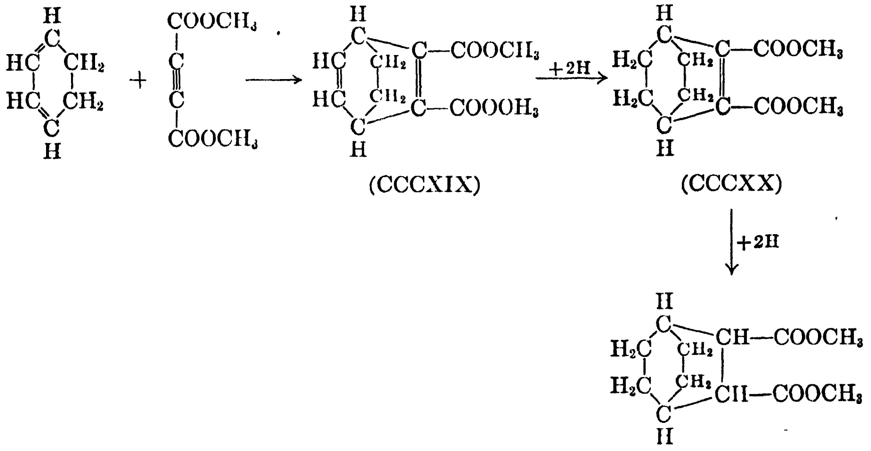
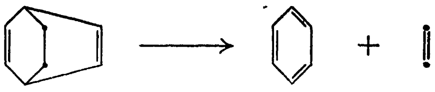
[259] Ziegler, Schenck, and Krochov, *Naturwissenschaften*, 29, 390 (1941); *Ann.*, 551, 1 (1942).



(CCCXIX) (CCCXX) (CCCXXI)

Another point of interest is the instability of the bicyclo-[2.2.2]-octadiene system (CCCXXII). Compounds of this type undergo a marked decomposition when heated. The ethylene bridge is eliminated from the bicyclic structure as olefin, and the peripheral ring is simultaneously aromatized (CCCXXIII)[260]:



(CCCXXII) (CCCXXIII)

This remarkable thermal dissociation has been used to prove the constitution of certain compounds, especially in the 1,3-cyclohexadiene series.[261–263] Addition of the 1,3-cyclohexadiene system to the acetylenic compound and subsequent decomposition of the adduct by heat proceeds very easily and is often carried out in one operation. The process may also be of occasional preparative value for the synthesis of substituted benzene derivatives. As acetylene components, only the esters of acetylenedicarboxylic acid have been used so far. In this case a phthalic acid ester and an olefin derivative are the products of the reaction. The following example illustrates the process:

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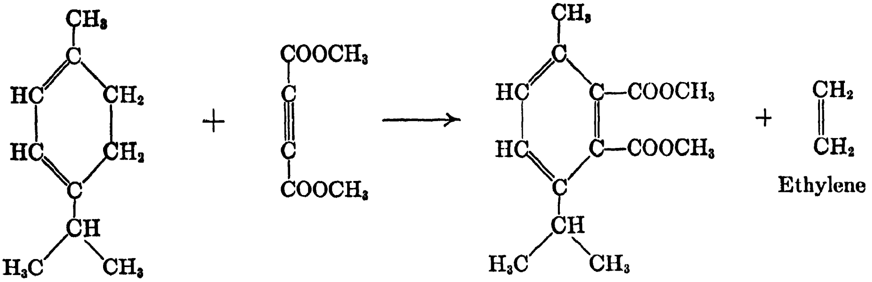
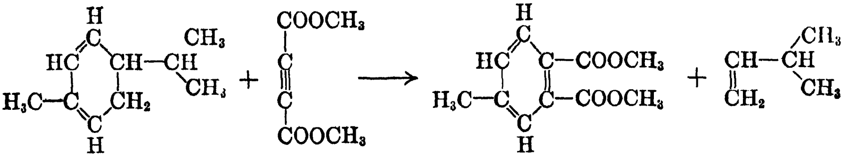
[260] Alder and Rickert, *Ann.*, **524**, 180 (1936); *Ber.*, **70**, 1354 (1937). Alder and Stein, *ibid.*, **62**, 2344 (1929).

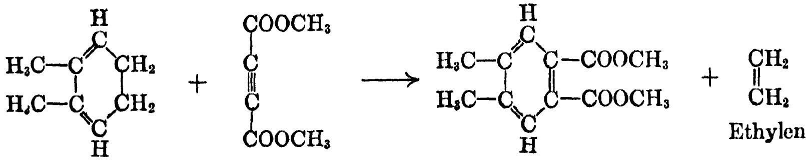


α-Terpinene Methyl-3-Methyl-6-isopropylphthalate Ethylene

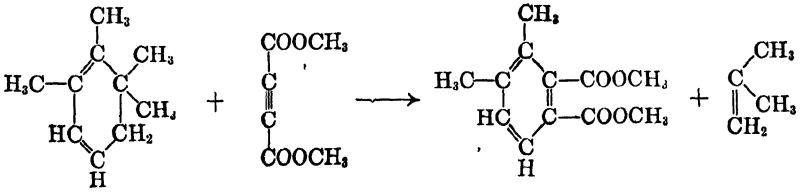


α-Phellandrene Methyl 4-methylphthalate Isopropylethylene

This reaction supplies direct proof of the structure of α-terpinene[264]:



2,3-Dimethyl-1,3-cyclohexadiene Methyl 4,5-dimethylphthalate Ethylene



β-Pyronene Methyl 3,4-dimethylphthalate Isobutylene

Other cases which demonstrate the applicability of the method are also indicated.[265]

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[261] Alder and Rickert, *Ber.*, **70**, 1364 (1937).

[262] Guillemonat, *Compt. rend.*, **206**, 1126 (1938); *Chem. Zentr.*, **1939**, I, 644; *Chem. Abstracts*, **32**, 4958 (1938).

[263] Dupont and Duloup, *Compt. rend.*, **201**, 219 (1935); **202**, 1861 (1936); *Angew. Chem.*, **51**, 755 (1938).

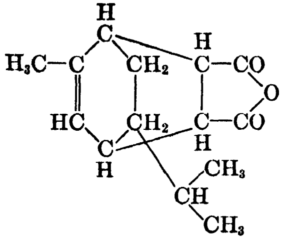
[264] Alder, *Ber.*, **71**, 2210 (1938).

[265] Concerning attempts to utilize the method with levopimaric acid, see Sandermann, *Ber.*, **74**, 154 (1941).

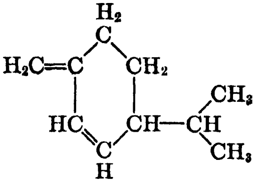
(*d*) *Cyclic Terpenes and Resin Acids; Use of Adducts of α-Terpinene and Abietic Acid with Maleic Anhydride in Lacquer Technology.* The behavior of the two monocyclic terpene hydrocarbons, $C_{10}H_{16}$, α-terpenene and α-phellandrene, toward the esters of acetylenedicarboxylic acid (see above) shows that these compounds first enter into a normal diene synthesis, and that at higher temperatures the adducts then undergo a characteristic thermal decomposition, which indicates the course of the reaction and the structure of the hydrocarbon.

In addition to the esters of acetylenedicarboxylic acid there is another series of α,β-unsaturated carbonyl compounds[266] to which both terpenes will add. Of these, only the reactions with maleic anhydride will be considered.

α-Phellandrene takes up this reactive addend in dilute solution with great ease to form a well defined addition product (CCCXXIV).[267-269] An analogous reaction with β-phellandrene (CCCXXV) leads only to amorphous products,[268,270] probably mixed polymers. The non-occurrence of a normal addition product with β-phellandrene was anticipated from earlier experience with the semicyclic arrangement of the conjugated system:



(CCCXXIV)



(CCCXXV)

Maleic anhydride adds to α-terpinene[271] with great ease. A conclusive proof of the constitution of the adduct has not yet been advanced, but from the foregoing observations there can be little doubt that it is 3-isopropyl-6-methyl-3,6-endoethylene-1,2,3,6-tetrahydrophthalicanhydride (CCCXXVI).

The same applies to a series of adducts of maleic anhydride with hydrocarbons which are analogues of α-terpinene (CCCXXVII) (R = H, $CH_2C_6H_5$, C_6H_5, β-$C_{10}H_7$):[270]

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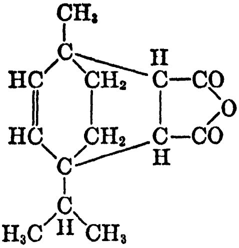
[266] Diels and Alder, *Ann.*, **470**, 67 (1929). Alder and Stein, *Ber.*, **62**, 2344, 2347 (1929).

[267] Diels and Alder, *Ann.*, **460**, 104 (1926).

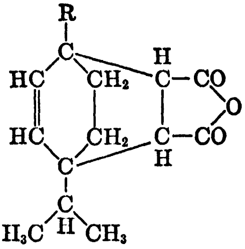
[268] Goodway and West, *J. Soc. Chem. Ind.*, **56**, 472 (1937); **57**, 37 (1938); *J. Chem. Soc.*, **1938**, 2028; *Nature*, **140**, 934 (1937).

[269] Littmann, *J. Am. Chem. Soc.*, **57**, 586 (1935); *Ind. Eng. Chem.*, **28**, 1150 (1936). Birch, *Proc. Roy. Soc., New South Wales*, **71**, 261 (1938); *Chem. Zentr.*, **1938,II**, 2756; *Chem. Abstracts*, **32**, 7666 (1938).

[270] Lipp-Bredt-Savelsburg and Steinbrink, *J. prakt. Chem.*, **149**, 107 (1937).



(CCCXXVI)



(CCCXXVII)

The adduct of α-terpinene and maleic anhydride has attained technical importance[272] in the synthesis of new alkyd resins. The types known so far, like the one from phthalic acid, are characterized by special properties. Apparently the introduction of substituents, such as —CH_3, —$CH(CH_3)_2$, and —CH_2—CH_2—, is responsible for these special properties and the resin types derived from them find application as raw materials for lacquers, varnishes, coating materials, and plastics. Increased resistance to light and weather, colorlessness and transparency even at elevated temperatures, greater hardness, and better oil compatability are cited as especially characteristic properties of these new compounds. Furthermore, the drying ability and film-forming ability should be increased if they are used in combination with drying oils.[273]

The addition of maleic anhydride to α-terpinene can be carried out in the presence of other terpenes, $C_{10}H_{16}$, which do not possess a system of conjugated double bonds.[274] However, these terpenes also react with maleic anhydride with formation of dicarboxylic acids. Consequently the quality of the product can be varied considerably by blending. Technically, this property is valued highly.

Finally, the synthesis of artificial resins by the principle indicated can be modified still further. The terpenes, $C_{10}H_{16}$, used as starting material can be mixed with natural resin acids with conjugated double bonds, which also undergo the diene synthesis. Thus, the nature of the end-product can be modified in a very desirable manner, so that various applications are possible.

The most important resin acids, which will be considered from the

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[271] Diels, Koch, and Frost, *Ber.*, 71, 1163 (1938). Sfirus, *Recherches (Roure-Bertrand fils)*, 1939, p. 115. Goodway and West, *J. Chem. Soc.*, 1940, 702.

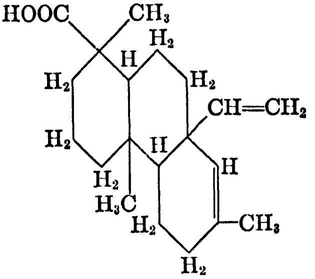
[272] Hercules Powder Co., U. S. Patents, 1,882,298, 1,993,025. The adduct (CCCXXVI) has the commercial designation "Petrex." Its esters with simple alcohols are active insecticides. Union Oil Co. and Merrill, U. S. Patent, 2,287,356.

[273] Littmann, *Chem.-Ztg.*, 60, 957 (1936); *Ind. Eng. Chem.*, 28, 1150 (1936).

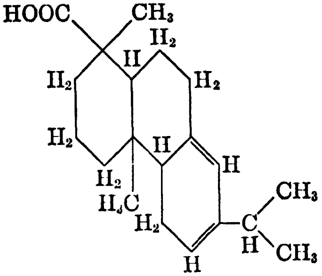
[274] Hercules Powder Co., U. S. Patent, 1,993,031 and numerous other patents. For the chemistry of these terpenes, which probably react by the scheme of "substituting addition," see Hultzsch, *Angew. Chem.*, 51, 920 (1938); *Ber.*, 72, 1173 (1939).

view-point of their adaptability to the diene synthesis, are dextropimaric (CCCXXVIII), levopimaric (CCCXXIX), and abietic acids (CCCXXX). The first two are natural resin acids, while the third represents a transformation product of levopimaric acid, and forms with great ease from the natural product by the influence of heat or by treatment with acids. Abietic acid is a constituent of technical rosin.

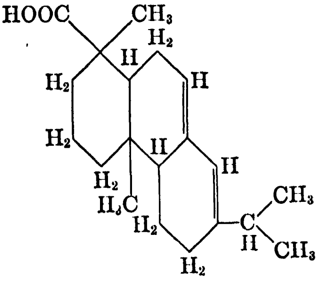
The formulas assigned to these acids at the present time show that the two double bonds are conjugated only in levopimaric and abietic acids. As would be expected, dextropimaric acid shows little incliniation to undergo the diene synthesis,[275] while the other two acids are thus qualified. The dienophile components, especially maleic anhydride, do not add to the acids with equal ease. While levopimaric acid enters into reaction in dilute solution with evolution of heat, abietic acid requires several hours heating at 150° to 160°C. The adducts formed from the two acids are identical (CCCXXXI)[275,276]:



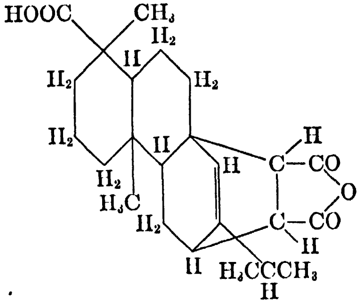
(CCCXXVIII)



(CCCXXIX)



(CCCXXX)



(CCCXXXI)

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[275] Ruzicka, Ankersmit, and Frank, *Helv. Chim. Acta*, **15**, 1289 (1932). Wienhaus and Sandermann, *Ber.*, **69**, 2202 (1936).

[276] Ruzicka and Bacon, *Helv. Chim. Acta*, **20**, 1542 (1937). Arbuzov, *J. Gen. Chem.* (*U. S. S. R.*), **2**, (64), 806 (1932); *Chem. Zentr.*, **1933**,II, 1192; *Chem. Abstracts*, **27**, 2688 (1933). Sandermann and Höhn, *Ber.*, **76B**, 1257 (1942).

This apparently remarkable behavior is in harmony with common experience and serves to broaden the stereochemical theory, which suggests that a conjugated system dispersed between two condensed rings, such as exists in abietic acid (CCCXXX), cannot undergo 1,4 addition which proceeds through ring formation.[277] Obviously, the heating causes a transposition of the conjugated system to the same position that it occupies in levopimaric acid. This also explains the ease with which the latter acid, in contrast to abietic, adds maleic anhydride as well as less active dienophiles like quinone[278] and α-naphthoquinone.[278]

The addition product of maleic anhydride with levopimaric or abietic acids has played an important role in the clarification of the structure of these acids.[279] Further, it should be pointed out that these diene syntheses have attained outstanding preparative interest, technically, in another connection.

The "maleic resins" developed from the tricarboxylic acid (CCCXXXI) belong, chemically, to the glyptal type. As oil-soluble artificial copals with especially valuable properties, they have demonstrated a wide range of applications.[280] In their excelling transparency and stability to light, in uniformity, and hardness, they are a very desirable supplement to the previously known artificial copal types.[281] The great preparative use that the diene synthesis exhibits in this field alone is best brought out by the fact that the production of maleic acid from coal must be increased both in Germany and America.

In practice the manufacture of these maleic resins is not carried out with the pure adduct (CCCXXXI) from maleic anhydride and levopimaric acid; but rosin, or rosin already contained in other artificial resin types in suitably blended proportions is combined with maleic acid or its anhydride and the reaction product subjected, sooner or later, to esterification with polyvalent alcohols, glycerol in particular. By incorporating drying or non-drying oils and by hydrogenation of the remaining double bonds numerous technical lacquers possessing valuable variations are possible.

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[277] Windhaus, *Nachr. Ges. Wiss. Gottingen, Math.-physik. Klasse., Fachgruppen*, 169 (1929); *Chem. Zentr.*, **1930,I**, 3194; *Chem. Abstracts*, **24**, 4518 (1930).

[278] Wienhaus and Sandermann, *Ber.*, **69**, 2202 (1936).

[279] Ruzicka *et al.*, *Helv. Chim. Acta*, **16**, 169 (1933); **20**, 1542 (1937); **21**, 583 (1938); **23**, 1346, 1357 (1940).

[280] See, for example, I. G. Farbenindustrie A.-G., French Patent, 711,924; *Chem. Zentr.*, **1932,I**, 143; *Chem. Abstracts*, **26**, 2072 (1932); Ellis-Forster Co., U. S. Patents, 2,063,540, 2,063,541, 2,063,542; *Chem. Zentr.*, **1937,I**, 2881, 3233; *Chem. Abstracts*, **31**, 894 (1937); Standard Oil Co., U. S. Patent, 2,063,369; *Chem. Zentr.*, **1937,I**, 2881, 3233; *Chem. Abstracts*, **31**, 850 (1937); Hercules Powder Co., U. S. Patent, 2,072,819; *Chem. Zentr.*, **1937,I**, 4162; *Chem. Abstracts*, **31**, 3175 (1937); 2,121,294; *Chem. Zentr.*, **1938,II**, 8326; *Chem. Abstracts*, **32**, 6360 (1938); I. G. Farbenindustrie A.-G., French Patent, 805,698; *Chem. Zentr.*, **1937,I**, 2032; *Chem. Abstracts*, **31**, 4421 (1937); Louis Blumer, German Patent, 662,384; *Chem. Zentr.*, **1939,I**, 262; *Chem. Abstracts*, **32**, 7609 (1938). Hovey and Hodgins, *Ind. Eng. Chem.*, **32**, 272 (1940).

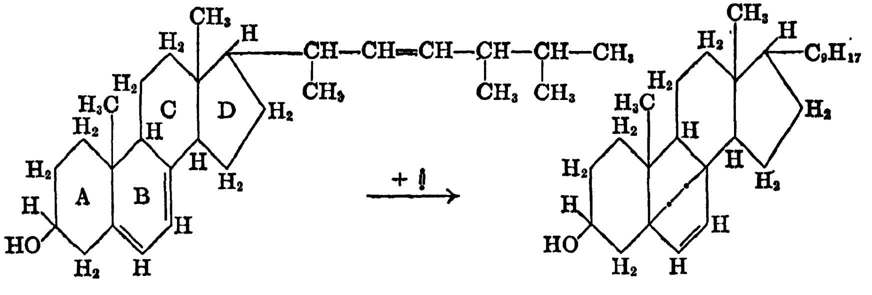
[281] Jordan, *Angew. Chem.*, **49**, 819 (1936). Fonrobert, *Chem.-Ztg.*, **63**, 137 (1939).

In lacquer technology the addition of maleic anhydride to abietic acid (rosin) has been carried out for the production of special effects, often with the simultaneous addition of terpene hydrocarbons (see above) and drying oil (see page 474). These various types of combinations are the subject of numerous patents.[282]

It has been suggested that the adducts from maleic anhydride and anthracene hydrocarbons, which will be discussed later (see page 485), may be useful in the field of synthetic resins.[283]

(*e*) *Sterol Series. Additions to Ergosterol Type.* Since the discovery that ergosterol is a provitamin D and that the physiological function depends on the existence of a system of conjugated double bonds, the diene synthesis has found various applications to the work in this field. Because the isomerization of ergosterol depends primarily on the displacement of its double bonds, the existing material on the subject is exceedingly extensive. The results obtained are not only of fundamental importance to the chemistry of steroids, but also add to the knowledge of the diene synthesis as applied to cyclic systems. This subject will be considered only from the second view-point.

Ergosterol has the constitution CCCXXXII.[284] Of the three double bonds, only two are in conjugated positions. They are contained in ring B. On this basis ergosterol is a derivative of 1,3-cyclohexadiene. Accordingly, application of the diene synthesis should produce the bicyclo-[2.2.2]-octane (CCCXXXIII).[277,285,286]



(CCCXXXII) (CCCXXXIII)

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[282] Hercules Powder Co., German Patent, 633,420; *Chem. Zentr.*, 1936,II, 3208; *Chem. Abstracts*, 30, 7725 (1936); U. S. Patent, 2,047,004; *Chem. Zentr.*, 1936,II, 3209; *Chem. Abstracts*, 30, 6089 (1936); 2,048,436; *Chem. Zentr.*, 1937,II, 1091; 2,067,859, 2,067,862; *Chem. Zentr.*, 1937,I, 3233; *Chem. Abstracts*, 31, 1519 (1937); 2,072,810, 2,072,818, 2,072,819; *Chem. Zentr.*, 1937,I, 4162; *Chem. Abstracts*, 31, 3175 (1937).

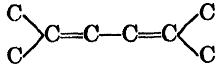
[283] Ardasehev and Bogatirev, Russian Patent, 53,396; *Chem. Zentr.*, 1939,I, 1666. Dubovski, Russian Patent, 53,143; *Chem. Abstracts*, 34, 5205 (1940).

[284] Lettré and Inhoffen, *Über Sterine, Gallensäuren und verwandte Naturstoffe*, Enke, Stuttgart, 1936, p. 123 ff.

[285] Windaus and Lüttringhaus, *Ber.*, 64, 850 (1931).

[286] Inhoffen, *Ann.*, 508, 81 (1934).

This conjugated system is characterized by the fact that it is totally substituted in the 1 and 4 positions, and thus belongs to the type:



It is remarkable that an acyclic molecule with this arrangement, obviously because of steric hindrance, does not undergo a diene synthesis, even with the most reactive olefins, such as maleic anhydride.[287] At any rate such additions have not been observed. On the other hand, ergosterol and other sterols with a similar location of the conjugated system, most suitably as their acetyl derivatives, add maleic anhydride under more or less forced conditions; namely, by heating the components in benzene or xylene solution for 8 hours at 135°C.

When heated, all the adducts of this type undergo a very smooth cleavage into the components. This thermal dissociation which is important from a preparative view-point (see below) is carried out most suitably in a high vacuum. Maleic anhydride or citraconic anhydride (which is often used) distils first, followed by the sterol or its acetyl compound.

Additions, similar to that described for ergosterol, can be carried out in an analogous manner with other compounds having the same arrangement of double bonds in ring B. Compounds of this group which undergo the diene synthesis with maleic and citraconic anhydrides to give adducts that are reversibly cleaved by heat are, as far as is known, all of the same type.

Recently,[288] three isomers of the ergosterol series, lumisterol,[289] pyrocalciferol,[290] and isopyrocalciferol,[291] have been examined in this connection. Certain information concerning the diene synthesis is derived from their study, because compounds containing all possible steric arrangements on the saturated carbon atoms of a 1,3-cyclohexadiene derivative can be prepared. Carbon atoms 9 and 10 which are not part of the conjugated system are asymmetric and are responsible for the existence of four stereoisomers (CCCXXXIV) which is realized in the compounds ergosterol, lumisterol, pyrocalciferol, and isopyrocalciferol.

The four stereoisomers show an analogous behavior in the diene synthesis. From this it follows that the steric arrangement of the substituents

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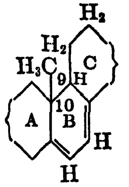
[287] See below, the behavior of dihydrotachysterol in the diene synthesis.

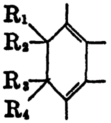
[288] For a compilation of the older methods, *cf.* Alder (foot-note 1), p. 3138 ff.

[289] Windaus, von Werder, and Lüttringhaus, *Ann.*, 499, 188 (1932).

[290] Müller, *Z. physiol. Chem.*, 233, 223 (1935).

[291] Windaus and Dimroth, *Ber.*, 70, 376 (1937). Dimroth, *ibid.*, 70, 1631 (1937). Windaus, Deppe, and Roosen-Runge, *Ann.*, 537, 1 (1939). Windaus, Dimroth, and Breywisch, *ibid.*, 543, 240 (1940). Heilbron, Kennedy, Spring, and Swain, *J. Chem. Soc.*, 1938, 869. Kennedy and Spring, *ibid.*, 1939, 250.

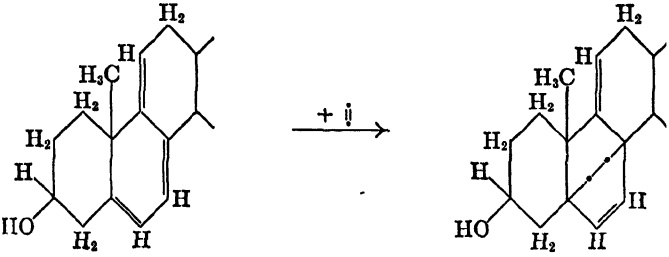

(CCCXXXIV)


(CCCXXXV)

(R_1, R_2, R_3, R_4) on the saturated carbon atoms of 1,3-cyclohexadiene derivatives (CCCXXXV) is not concerned in the diene synthesis.

In addition to ergosterol and its isomers, two other sterols with a similar arrangement of the double bonds in ring B have been investigated: 7-dehydrocholesterol,[292,293] (provitamin D_3), and 7-dehydrositosterol.[294] The addition of maleic anhydride to these compounds is rather difficult. It proceeds under the same conditions specified above for the ergosterol type.

It is remarkable that dehydroergosterol (CCCXXXVI), which has a system of conjugated double bonds divided between rings B and C, adds maleic anhydride, even at room temperature. By heating for 4 hours in benzene solution a quantitative yield of the addition product is obtained.[295,296]


(CCCXXXVI) (CCCXXXVII)

Undoubtedly, the addition takes place to the double bonds of ring B and gives the compound (CCCXXXVII). This is positively shown by the fact that the hexahydro derivative, which results when the dehydroergosterol acetate-maleic anhydride adduct is catalytically reduced (with simultaneous saturation of the side chain), is identical with the adduct from tetrahydroergosterol acetate and maleic anhydride.[296] Besides, the

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[292] Windaus, Lettré, and Schenck, *Ann.*, 520, 98 (1935). Schenck, Buckholz, and Wiese, *Ber.*, 69, 2696 (1936).

[293] Diene synthesis of isodehydrocholesterol with other double bond compounds can only be referred to here; see Windaus, Linsert, and Eckhardt, *Ann.*, 534, 22 (1938); Windaus and Zühlsdorff, *ibid.*, 536, 204 (1938).

[294] Wunderlich, *Z. physiol. Chem.*, 241, 123 (1936).

[295] Windaus and Lüttringhaus, *Ber.*, 64, 850 (1931).

[296] Honigmann, *Ann.*, 508, 89 (1934).

course of this addition is in complete agreement with the generally accepted theory, that diene syntheses with hexatrienes (three conjugated double bonds) do not take place in the 1,6 position (see page 388). Furthermore, on stereochemical grounds, no ring closure which proceeds through 1,4 addition can take place in a condensed ring system in which the conjugated double bonds are divided between two rings (see page 383). The addition of maleic anhydride to dehydroergosterol must, therefore, proceed according to the mechanism formulated above, CCCXXXVI → CCCXXXVII. The increased velocity of addition that dehydroergosterol (CCCXXXVI) shows over ergosterol (CCCXXXII) is surprising.

The analogy shown in the synthesis of the two adducts, CCCXXXIII and CCCXXXVII, is again demonstrated by their behavior toward heat. Dehydroergosterol acetate-maleic anhydride, like ergosterol acetate-maleic anhydride, decomposes into its components at 240°C.

Synthesis of 22-Dihydroergosterol by Reversible Blocking of Conjugated System. The thermal dissociation of maleic anhydride adducts to sterols of the type of ergosterol possesses preparative importance. In all reactions which take place at the double bonds, such as catalytic hydrogenation, oxide formation, etc., the double bond which joins carbon atoms 22 and 23 (in the side chain) reacts at the same time as the double bonds of ring B. Consequently, a uniform course of reaction, which is necessary for preparative purposes, cannot be obtained. By the addition of maleic anhydride, however, the double bond system in ring B can be temporarily eliminated, and a reaction can now be effected with the double bond in the side chain. When this reaction is complete, the maleic anhydride can be removed by heating, thus regenerating the conjugated system originally present in ring B.

In this manner, ergosterol (CCCXXXII) can be selectively hydrogenated to 22-dihydroergosterol (CCCXXXIX, R = H), provitamin D_4.[297] When ergosterol acetate (CCCXXXVIII) is catalytically hydrogenated, the first mole of hydrogen is added in ring B, but addition of H to the adduct with maleic anhydride is in the side chain exclusively. Thermal cleavage of the resulting hydrogenated adduct gives 22-dihydroergosterol acetate (CCCXXXIX, R = $COCH_3$).

By use of this procedure, 22-dihydroergosterol, which is not accessible in a direct manner, can be prepared rather easily. Information derived from its study was particularly valuable in determining the relationship between physiological activity and the location of the double bond.

It must be emphasized that the thermal cleavage proceeds smoothly, only when the new double bond, formed in ring B as a result of the diene

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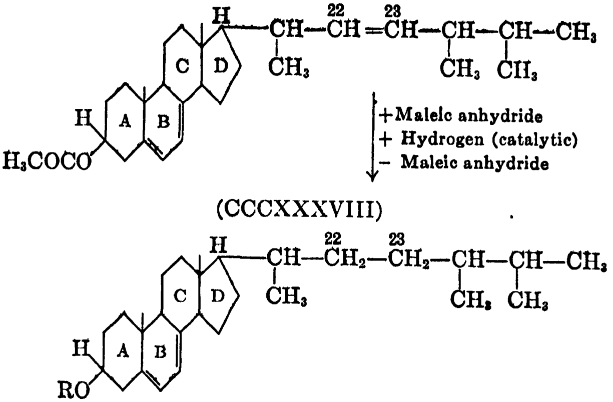
[297] Windaus and Langer, *Ann.*, 508, 105 (1934). Windaus and Inhoffen, *ibid.*, 510, 260 (1934).



(CCCXXXVIII)

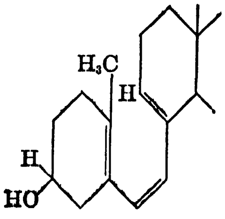
(CCCXXXIX)

synthesis with maleic anhydride, is still present. If the hydrogenation of the ergosterol acetate-maleic anhydride adduct is carried beyond the dihydro compound to the tetrahydro product, such a thermal dissociation is no longer feasible.[286]

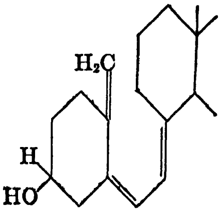
The synthesis of 22,23-ergosterol oxide has been accomplished in a manner similar to the preparation of 22-dihydroergosterol; namely, by an intermediate protection of the double bonds in ring B. The action of active oxygen on the maleic anhydride addition product, like that of catalytic hydrogen, is directed primarily to the side chain.[298]

Fractional Diene Synthesis; Isolation of Vitamin D. As is known, the irradiation of ergosterol results in the formation of a series of photo isomers, thus: ergosterol → lumisterol → tachysterol → vitamin D_2 → suprasterol I and II.

The behavior of ergosterol and lumisterol in the diene synthesis has already been discussed in the previous section. Suprasterol I and II possess no conjugated double bonds and are therefore eliminated from a place in this discourse. On the other hand, the very characteristic and thoroughly studied behavior of tachysterol (CCCXL) and vitamin D_2



(CCCXL)



(CCCXLI)

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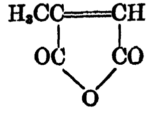
[298] Buckholz, Dissertation, Göttingen (1937).

(CCCXLI) toward the diene synthesis must be described here, for it is responsible for preparative advancements in this field.

Strictly speaking, diene syntheses with tachysterol and vitamin D_2 should not be included here, because these substances are not 1,3-cyclohexadiene derivatives and do not lead to the bicyclo-[2.2.2]-octane type. Nevertheless, their reactions will be considered because of their close relationship with the foregoing.

They are formed from ergosterol and lumisterol by the opening of ring B and the formation of a new double bond. It is known that the isolation of vitamin D_2 from the irradiation products of ergosterol offers considerable difficulty on account of the presence of the very unstable tachysterol. In the chemistry of the D vitamins the smooth and careful removal of tachysterol is often necessary. It can be solved in an ideal manner by the use of the diene synthesis, if the following facts are considered. Of the photoisomers of ergosterol, all except suprasterol I and II possess a system of at least two conjugated double bonds. All are suitable for the addition of maleic anhydride. However, the additions proceed with markedly different velocities. This difference has been applied to their separation with great success. As was mentioned above, ergosterol and lumisterol react very slowly with maleic anhydride at high temperatures (140°C.). At room temperature practically no addition results. Tachysterol, on the other hand, adds rapidly at room temperature, while vitamin D_2 occupies an intermediate position. In order to broaden further the difference in additive power of tachysterol and vitamin D_2 the use of the slower adding citraconic anhydride in place of the highly reactive maleic anhydride has been recommended. The velocities of addition of the various dienes with this compound differ so markedly that a separation is possible.



This process of separation by "fractional diene synthesis" has found general application in the field of the D vitamins. It has been utilized with success for the preparation of the pure vitamins D_1, D_2, D_3, and D_4 from the mixture obtained by irradiation of their provitamins, ergosterol, 7-dehydrocholesterol, and 22-dihydroergosterol.[299] With its aid it is possible at times to separate the very reactive tachysterol, despite extreme sensitiveness, without attacking the D vitamin. After this preliminary treatment the isolation of the D vitamin can be accomplished without difficulty by the use of other suitable methods.

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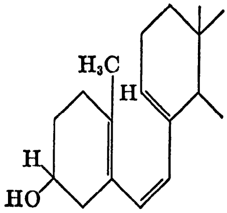
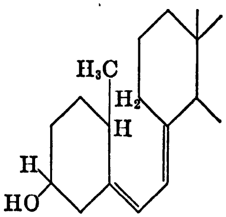
[299] Application to vitamins D_1 and D_2 [Windaus, Lüttringhaus, and Deppe, *Ann.*, 489, 252 (1931); Windaus, Linsert, Lüttringhaus, and Weidlich, *ibid.*, 492, 229 (1932)]. Application to vitamin D_3 [Windaus, Schenck, and von Werder, *Z. physiol. Chem.*, 241, 100 (1936); Merck, British Patent, 491,653; *Chem. Zentr.*, 1939,I, 184); *Chem. Abstracts*, 33, 1105 (1939). Application to vitamin D_4 Windaus and Trautmann, *Z. physiol. Chem.*, 247, 185 (1937); Windaus and Guntzel, *Ann.*, 538, 120 (1939)].

Since the tachysterol-citraconic anhydride adduct decomposes readily in a high vacuum at 165°C. into its components,[289] the method has been used to prepare this sensitive sterol.[300] Unfortunately the most plausible formula (CCCXL) for tachysterol is still uncertain and details concerning the course of the addition should be investigated. Its extremely great velocity of reaction in the diene synthesis, the ability of its adducts to decompose by heating (differing from the vitamin D adducts), and the inability of its dihydro compound (CCCXLII)[301] to enter into diene syntheses are interesting and remarkable facts:

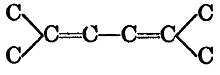


(CCCXL)



(CCCXLII)

A comparison of dihydrotachysterol (CCCXLII) with ergosterol (CCCXXXII) indicates that the additive ability of conjugated systems having the same degree of substitution,



$$\begin{matrix} C & & C \\ & \!\!>C{=}C{-}C{=}C<\!\! & \\ C & & C \end{matrix}$$

and the same location in the molecule, depends, decisively, upon whether such a formation is or is not part of a ring.

Course of Diene Synthesis with Vitamin D_2. While certain phases of the addition of maleic anhydride or citraconic anhydride to tachysterol still remain an open question, the diene reaction on vitamin D_2 is well known.[302,303]

The addition of maleic anhydride to the acetyl derivative of the vitamin is brought about by heating the components in benzene solution under a reflux for 4 hours. The addition proceeds quantitatively under these conditions. As has been emphasized above, addition occurs more easily than with ergosterol and more difficultly than with tachysterol. The transformation product of vitamin D_2 consists of two substances which are apparently related to each other as stereoisomers, since they behave the same on degradation.[302] The results of this degradation not only make clear the course of the addition of maleic anhydride, but, at the same time, offer the most important support for the formulation of vitamin D_2.

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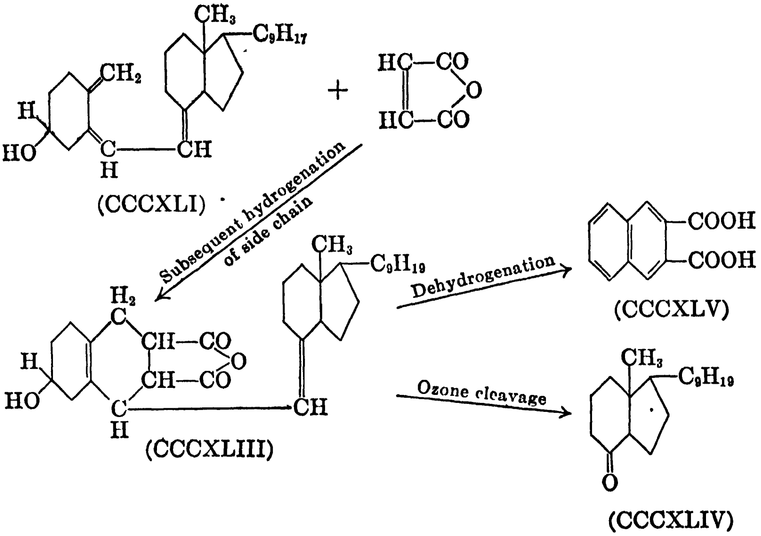
[300] Grundmann, Dissertation, Göttingen (1938); *Z. physiol. Chem.*, **252**, 151 (1938).

[301] Von Werder, *Z. physiol. Chem.*, **260**, 119 (1939).

[302] Windaus and Thiele, *Ann.*, **521**, 160 (1936).

[303] Windaus and Grundmann, *Ann.*, **524**, 295 (1936).



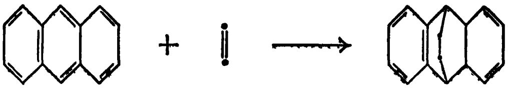
In accordance with the general rule, the hexatriene system adds to vitamin D_2 (CCCXLI), not as a whole (1,6 addition), but in the 1,4 position with the formation of a new six-membered ring. That this addition, which may, *a priori*, take place in two ways, occurs exclusively on the free (*i.e.*, unsubstituted) end of the hexatriene system, in accordance with the rule, is unequivocally confirmed by the degradation of the adduct. The double bond in the side chain is saturated by partial catalytic hydrogenation. The dihydro compound (CCCXLIII) on dehydrogenation yields a naphthalene derivative; *i.e.*, with palladium-charcoal 2,3-naphthalic acid (CCCXLV) is formed in addition to some naphthalene. By cleavage with ozone, CCCXLIII is transformed into a ketone (CCCXLIV) which, without doubt, contains rings C and D of ergosterol unchanged.

Since the adduct, vitamin D_2-maleic anhydride, is derived from an acyclic diene, it is distinguished by its exceptional stability. It may be distilled without decomposition at 255° to 260°C. at 0.001 mm. pressure. In this it differs from the analogous compounds of the ergosterol series (see above).

The degradation reactions of these adducts which have been exhaustively investigated (especially in the case of vitamin D_2) are undoubtedly applicable to vitamins D_3 and D_4. The latter differ from vitamin D_2 only in the structure of the side chain; the conjugation is the same, however, and considered from the standpoint of the diene synthesis, therefore, they offer nothing new.[304,305]

(*f*) *Anthracene and Other Polynuclear Aromatic Compounds.* Attempts to use the double bond system of an aromatic nucleus as a diene component are very numerous. No positive results have been obtained in a diene synthesis either with benzene or its simple homologues[306] or with naphthalene,[307] phenanthrene,[308] chrysene,[309] or pyrene.[310]

The presence of at least three linear, fused aromatic nuclei must be regarded as the *conditio sine qua non* for the inception of reaction. Anthracene, its homologues, and derivatives, as well as numerous benzo derivatives of anthracene, are very reactive partners in the diene synthesis. The olefin or acetylene components add without exception to the conjugated system of the central nucleus; thus, the addition to anthracene is in the 9,10 position.[311] The addition products are regarded as benzo derivatives of bicyclo-[2.2.2]-octane (CCCXLVI):



(CCCXLVI)

The velocity of this addition is dependent upon the nature of the substituents in the 9,10 positions of the anthracene system.[312–319] The methyl

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[304] Windaus, Deppe, and Wunderlich, *Ann.*, **533**, 118 (1938).

[305] Windaus and Trautmann, *Z. physiol. Chem.*, **247**, 185 (1937). Windaus and Güntzel, *Ann.*, **538**, 120 (1939).

[306] The addition of benzene homologues, like ethylbenzene, isopropylbenzene, etc., with α,β-unsaturated dianhydrides is not a diene synthesis, but a "substituting addition" which proceeds with the displacement of hydrogen. Binapfl and I. G. Farbenindustrie A.-G., German Patents, 607,380, [*C. A.* **29**, 1834 (1935)] 623,338 [*C. A.* **30**, 2205 (1936)].

[307] The reaction of naphthalene with maleic anhydride according to French Patent, 636,065 [*C. A.* **25**, 4537 (1931)] and German Patent, 554,879 [*C. A.* **26**, 6155 (1932)] belongs to the Friedel-Crafts type.

[308] Clar, *Ber.*, **65**, 853 (1932). The statement in *Chem. Zentr.*, **1932,I**, 1952 needs a correction.

[309] Clar and Lombardi, *Ber.*, **65**, 1413 (1932).

[310] Clar, *Ber.*, **69**, 1683 (1936).

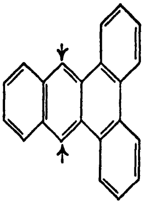
[311] I. G. Farbenindustrie A.-G., Kalischer and Scheyer, German Patent, 499,590; *Chem. Zentr.*, **1930,II**, 1136; *Chem. Abstracts*, **24**, 4522 (1930); German Patent, 539,832; *Chem. Zentr.*, **1932,I**, 1952; *Chem. Abstracts*, **26**, 2201 (1932). Diels and Alder, *Ann.*, **486**, 191 (1931). Clar, *Ber.*, **64**, 1676, 2194 (1931). Barry Barnett *et al.*, *J. Chem. Soc.*, **1934**, 1224. *Cf.* also the monograph by Alder (foot-note 1), p. 3099 ff.

[312] Clar, *Ber.*, **64**, 2194 (1931).

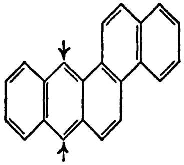
[313] Bachmann and Kloetzel, *J. Org. Chem.*, **3**, 55 (1938).

[314] Bachmann and Chemerda, *J. Am. Chem. Soc.*, **60**, 1023 (1938).

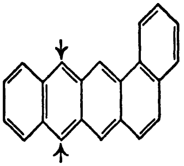
group greatly facilitates the addition, while phenyl and halogen act as inhibitors. The position of other aromatic nuclei fused to the anthracene system also has an influence on the velocity of addition. A benzene ring attached in the 1,2 position of anthracene suppresses the additive power, while a 2,3 attachment promotes it. For example, in the three hydrocarbons, CCCXLVII, CCCXLVIII, and CCCXLIX, the rate of addition increases so greatly, as indicated in the accompanying sequence, that a "fractional diene synthesis" can be used for their separation[320]:



(CCCXLVII)

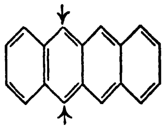


(CCCXLVIII)

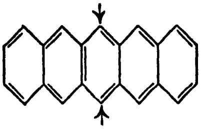


(CCCXLIX)

The velocity of addition increases with the number of linear fused nuclei; 2,3,6,7-dibenzanthracene (CCCLI) reacts instantaneously with maleic anhydride,[312,321] while 2,3-benzanthracene (CCCL) has a reactivity intermediate between that of anthracene and pentacene (CCCLI)[321]:



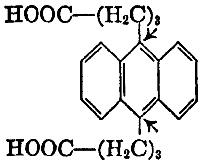
(CCCL)



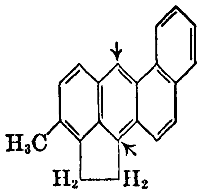
(CCCLI)

The reaction is very broad in scope with regard to both the anthracene derivative and the dienophile component. In addition to the anthracene type mentioned above, five compounds are shown for comparison:

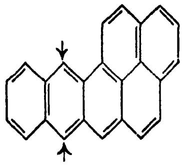
[315] Dufraisse *et al.*, *Bull. soc. chim. France*, 5, 1073 (1938).
[316] Willemart, *Bull. soc. chim. France*, 6, 204 (1939).
[317] Bergmann and Bergmann, *J. Am. Chem. Soc.*, 62, 1699 (1940).
[318] Bartlett and Cohen, *J. Am. Chem. Soc.*, 62, 1183 (1940).
[319] Bachmann and Kloetzel, *J. Am. Chem. Soc.*, 60, 481 (1938).
[320] Clar and Lombardi, *Ber.*, 65, 1418 (1932); compare the previous section.
[321] Clar, *Ber.*, 65, 503 (1932).
[321a] Beyer, *Ber.*, 70, 1105 (1937).
[321b] Clar, *Ber.*, 69, 1671 (1936).



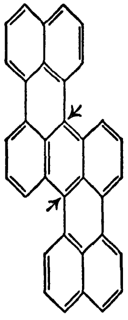
Anthracene-9,10-dibutyric acid[321a]



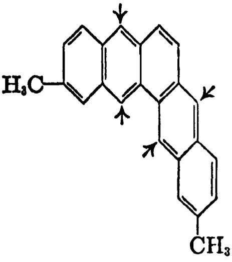
Methylcholanthrene[319]



Naphtho-2′,3′,3,4-pyrene[321b]



1,9,5,10-Di [perinaphthylene] anthracene[333]



7,7′-Dimethyl [naphtho-2′,3′,1,2-anthracene][312]

All five compounds contain the anthracene ring and add in the central nucleus, as indicated by the arrows. It is noteworthy that the last hydrocarbon shown adds twice. The reaction has proved unusually flexible, particularly with respect to the choice of the olefin component. Maleic anhydride,[322] which has been used most frequently, may be replaced by quinone,[323] dibromomaleic anhydride,[322] crotonic acid,[322] acrylic acid,[324] cinnamic acid,[324] methylenemalonic ester,[325] acetylenedicarboxylic ester,[191,326] acrolein,[327] allyl alcohol,[328] vinyl acetate,[329] indene,[330] azodicarboxylic ester,[331] fumaronitrile,[188] and other unsaturated compounds including ethylene and cyclohexene.[332]

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[322] Diels and Alder, *Ann.*, **486**, 191 (1931).

[323] Clar, *Ber.*, 64, 1676 (1931). Kremann *et al.*, *Monatsh.*, **43**, 269 (1922).

[324] I. G. Farbenindustrie A.-G., Kalischer and Scheyer, German Patents, 499,590, and 539,832; *Chem. Zentr.*, **1930,II**, 1136 and **1932,I**, 1952; *Chem. Abstracts*, **24**, 4522 (1930) and *Chem. Abstracts*, 26, 2201 (1932).

[325] Eastman Kodak Co., Bachmann and Tanner, U.S. Patent, 2,212,506.

[326] Diels and Friedrichsen, *Ann.*, **513**, 145 (1934).

[327] Slobodskoi and Chmelewski, *J. Gen. Chem.* (*U. S. S. R.*), **10**, (72), 1199 (1940); *Chem. Zentr.*, **1941,I**, 2939; *Chem. Abstracts*, **35**, 2883 (1941).

[328] Alder and Windemuth, *Ber.*, **71**, 1941 (1938).

[329] Alder and Rickert, *Ann.*, **543**, 9 (1940).

[330] Mameli, *Gazz. chim. ital.*, **67**, 669 (1937).

[331] Diels, Schmidt, and Witte, *Ber.*, **71**, 1186 (1938).

[332] Thomas, U.S. Patent, 2,406,645 (1946); *Chem. Abstracts*, **41**, 487 (1947).

The addition results when the components are heated in a melt or in an indifferent solvent. The reversibility of the addition must be considered in all these cases (see the following).

In all instances the addition follows the same course. According to the general scheme given above, the olefin or acetylene component is introduced as a bridge in the central ring of the anthracene with the formation of a bicyclo-[2.2.2]-octane system. This type of compound was unattainable before the advent of the diene synthesis, and its preparation by this procedure is a notable contribution to the field of organic synthesis. Another useful property derives from the fact that the adduct can be dissociated into its component parts by heat.

In the anthracene series this dissociation often takes place at temperatures which are necessary to attain a reasonably rapid union of the components; that is, an equilibrium[312,314,319,333] is formed which is dependent not only on the temperature[334] and solvent, but primarily on the nature of the substituents.

For preparative purposes, this information must be taken into account, particularly in those cases in which the equilibrium is predominantly on the side of the components under the usual conditions of the diene synthesis. The use of a large excess of one of the two addends and the choice of a lower boiling solvent are often of vital importance.[319]

The position of the equilibrium, maleic anhydride + anthracene derivative ⇌ adduct, has been investigated in a few cases. The following table shows the maximum yields of adduct observed with equimolecular quantities of the components at the same initial concentration (0.1 g. of hydrocarbon) in boiling xylene (2 ml.).

Anthracene	99%	9,10-Diphenylanthracene	16%
9-Methylanthracene	99%	1,2-Benzanthracene	84%
9,10-Dimethylanthracene	98%	1,2,5,6-Dibenzanthracene	30%
9-Phenylanthracene	75%	3-Methylcholanthrene	22%

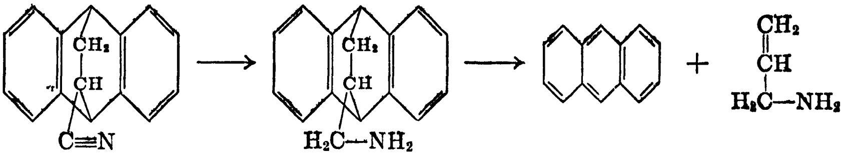
By the use of thirty moles of maleic anhydride to one mole of hydrocarbon in the same solvent, the yield of adduct is increased as follows: 9-phenylanthracene 97%, 9,10-diphenylanthracene 78%, 1,2-benzanthracene 99%, 1,2,5,6-dibenzanthracene 91%, 3-methylcholanthrene 83%. The addition of maleic anhydride to methylcholanthrene shows the influence of temperature on the reaction. From equimolecular quantities of the two components in boiling benzene a high yield (94%) of addition product is produced, while the equilibrium concentration of the adduct in boiling xylene amounts to only 22%.

[333] Clar and Guzzi, *Ber.*, 65, 1521 (1932).

[334] Since the additions proceed exothermically, increasing temperature tends to break down the addition product into its components.

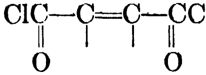
As in the sterol series, the reversible dissociation of the anthracene adduct offers many new synthetic possibilities. Thus, it is possible, by the addition of unsaturated compounds to anthracene, to inactivate the double or triple bond and to protect it from undesirable chemical reactions.

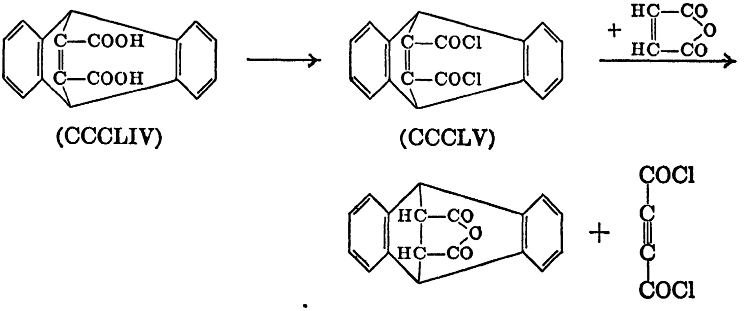
For example, the conversion of acrylonitrile to allylamine is accomplished by reduction of the nitrile group in the adduct (CCCLII) of the unsaturated nitrile and anthracene, followed by thermal decomposition of the resulting primary amine (CCCLIII) into allylamine and anthracene:



(CCCLII) (CCCLIII)

The diene synthesis may be used with advantage in the preparation of the dichloride of acetylenedicarboxylic acid.[335] This acid chloride was previously unknown and could not be obtained directly from the acid, since the hydrogen chloride which was formed simultaneously added to the exceptionally reactive triple bond. The addition of acetylenedicarboxylic acid to anthracene yields the "endomaleic acid" (CCCLIV), which can be converted in the usual manner to its stable dichloride (CCCLV). The simple thermal cleavage of the latter compound is not successful in this case, owing to the sensitivity of the dichloride of acetylenedicarboxylic acid toward heat. Instead, the chloride may be secured by displacing the meso bridge, $\underset{\underset{O}{\|}}{ClC}—\underset{|}{C}=\underset{|}{C}—\underset{\underset{O}{\|}}{CCl}$, with the very reactive maleic anhydride:





(CCCLIV) (CCCLV)

The addition of maleic anhydride to anthracene and highly condensed hydrocarbons is also used for the isolation and purification of these aromatic compounds.[336] As acids, the adducts are separated easily from the unchanged hydrocarbons, and the aromatic components and maleic anhydride are regenerated in the pure form by heating. For this reason, the method also has been suggested for the purification of the anhydride.[337] Needless to say, the principle of "fractional diene synthesis" can be employed here, as in the sterol series, in further development of this procedure.[338]

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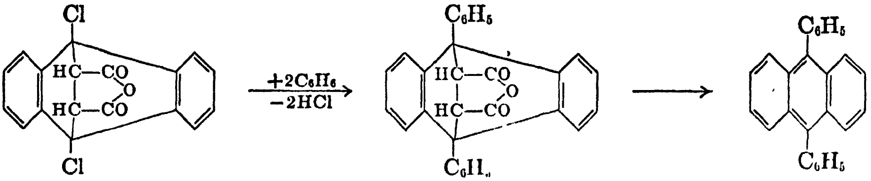
[335] Diels and Thiele, *Ber.*, 71, 1173 (1938).

In a similar manner, the tendency of the anthracene hydrocarbons to undergo addition is utilized for the separation of the "chrysogens," which occur as impurities in the higher coal tar hydrocarbons and are usually removed only with great difficulty. The purification is accomplished readily by the use of maleic anhydride. Thus, the commercial grade of chrysene can be decolorized by a brief treatment with maleic anhydride in boiling xylene. The contaminant of chrysene, the orange-colored 2,3-benzanthracene (naphthacene) (CCCL) adds, while chrysene itself undergoes no change.[339]

A further use of the diene synthesis, which illustrates another phase of its versatility, is found in the preparation of derivatives of anthracene which are halogenated in the meso position.[340] In these compounds the halogen is present in aromatic combination and, therefore, not available for many reactions. Thus, the synthesis of 9,10-diphenylanthracene from 9,10-dichloroanthracene and benzene by the Friedel-Crafts reaction is not possible. The addition of maleic anhydride to 9,10-dichloroanthracene (CCCLVI) deprives the carbon atoms in the 9,10 positions of their aromatic character, thus increasing the reactivity of the chlorine atoms and making them replaceable. The reaction product (CCCLVII) which is expected, immediately splits out maleic anhydride under the conditions of the reaction and is converted to 9,10-diphenylanthracene (CCCLVIII):



(CCCLVI) (CCCLVII) (CCCLVIII)

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[336] Postovski, Ardaschev, and Chmelevski, Russan Patent, 52,391; *Chem. Zentr.*, 1938,II, 952; *Chem. Abstracts*, 34, 3055 (1940).

[337] Hercules Powder Co. and Littmann, U. S. Patent, 2,150,331.

[338] Clar and Lombardi, *Ber.*, 65, 1411 (1932).

[339] Clar and Lombardi, *Ber.*, 65, 1413 (1932). Cook, Hewett, and Hieger, *J. Chem. Soc.*, 1933, 395. *Cf.* Clar, *Ber.*, 65, 1426 (1932).

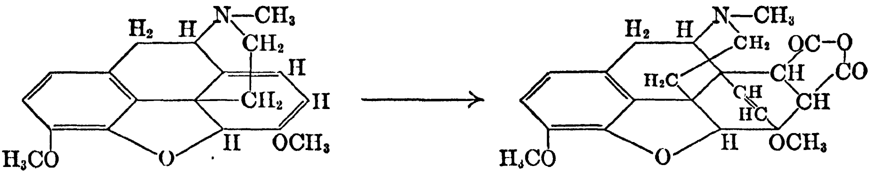
[340] Clar, *Ber.*, 64, 2200 (1931).

The meso-arylated anthracenes which are obtained in this manner can also be synthesized by means of the Grignard reaction on anthraquinone. Consequently the new method is of greatest value for the introduction of aryl groups whose Grignard complexes are difficult to prepare.

It has recently been shown that the analogous 1-azaanthracene adds maleinimide[341] in the same manner as maleic anhydride adds to anthracene. 2,3,9-Trimethyl-1-azaanthracene is said to undergo a similar reaction with maleic anhydride.[342]

(*g*) *Nitrogen-Containing Hexacyclic Dienes*; *Additions to Thebaine and Dihydropyridine.* While phenanthrene does not undergo the diene synthesis, partially hydrogenated phenanthrene derivatives which possess a pair of conjugated double bonds react normally with dienophiles. This tendency remains undiminished even when there are complicating factors, such as a high degree of substitution in the hydrophenanthrene system.

This fact is well illustrated by an example of the diene synthesis with thebaine (CCCLIX) and maleic anhydride or quinone.[343,344] As with the simple 1,3-cyclohexadiene derivatives, the bicyclo-[2.2.2]-octane system is formed:



(CCCLIX) (CCCLX)

Space does not permit a thorough treatment of the maleic anhydride-thebaine reaction product (CCCLX) which has been of such value in the location of the conjugated system in thebaine.[344] Likewise, the remarkable transformation of thebaine-quinone which reveals the influence of the N atoms on the oxygen of the quinone component must be omitted.

The derivatives of α-dihydropyridine (CCCLXI) represent another type of nitrogen compound which contains a pair of conjugated double bonds in a six-membered ring. They are obtainable in the usual manner by the diene synthesis,[345] as illustrated by the reaction of *N*-methyl-α-dihydro-γ-phenyllutidinedicarboxylic ester (CCCLXII) with maleic anhydride. The peripheral ring, which is formed in the addition, is carbocyclic[346] and 1 of the carbon atoms of the "ethylene bridge" of the bicyclo-[2.2.2]-octane (CCCLXIII) is replaced by nitrogen:

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[341] Etienne, *Ann. chim.*, 1, 4 (1946).

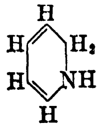
[342] Johnson and Matthews, *J. Am. Chem. Soc.*, 66, 210 (1944).

[343] Sandermann, *Ber.*, 71, 648 (1938).

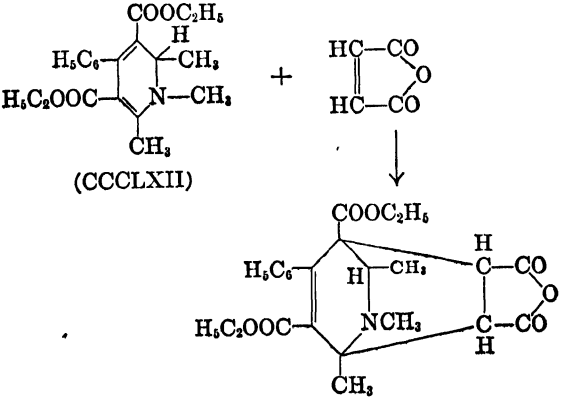
[344] Schöpf, von Gottberg, and Petri, *Ann.*, 536, 216 (1938).

[345] Mumm and Diedrichsen, *Ann.*, 538, 201 (1939).

[346] It is for this reason that these compounds are mentioned here. The formation of heterococylic rings by addition is the subject matter of a later section (see p. 501).



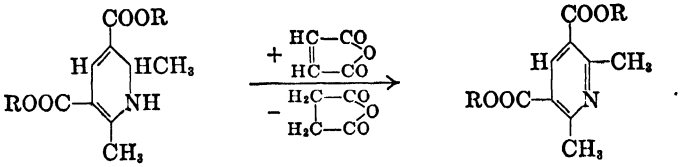
(CCCLXI)



(CCCLXII)

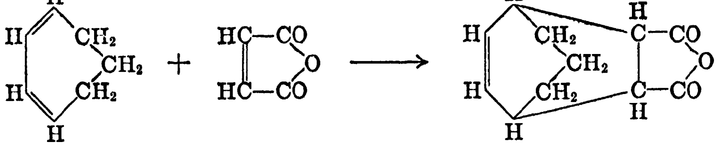
(CCCLXIII)

If the derivative of α-dihydropyridine carries a free hydrogen on the nitrogen, dehydrogenation occurs. Maleic anhydride acts as the hydrogen acceptor and succinic anhydride is formed in addition to the pyridine derivative. This case is illustrated by the addition of maleic anhydride to α-dihydrolutidinedicarboxylic ester (CCCLXIV)[347]:



(CCCLXIV)

(3) Bicyclo-[3.2.2]-nonane Series. The synthesis of this previously unknown bicyclic ring system can be achieved by the addition of activated olefins to the derivatives of 1,3-cycloheptadiene. For example, maleic anhydride adds to 1,3-cycloheptadiene (CCCLXV),[348] to give 3,6-endopropylene-1,2,3,6-tetrahydrophthalic anhydride (CCCLXVI):



(CCCLXV) (CCCLXVI)

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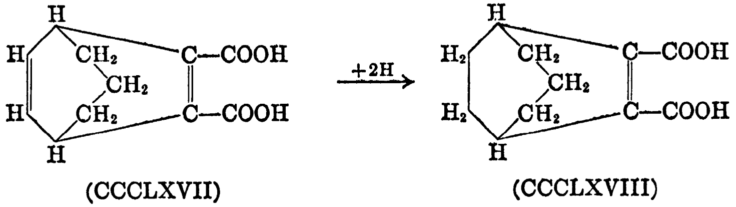
[347] Mumm and Diedrichsen, *Ann.*, **538**, 229 (1939).

[348] W. Koch, Dissertation, Kiel (1932).

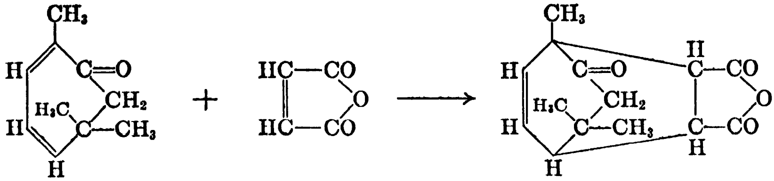
[349] Kohler *et al.*, *J. Am. Chem. Soc.*, **61**, 1057 (1939), describe the addition of maleic anhydride to 1,3,5-cycloheptatriene.

Because of its relative inaccessibility, very little information has been obtained about 1,3-cycloheptadiene. However, all observations seem to indicate that the addition is *normal* in this series.[349] Thus, the doubly unsaturated 3,6-endopropylene-3,6-dihydrophthalic acid (CCCLXVII) is obtained from 1,3-cycloheptadiene and acetylenedicarboxylic acid. Partial hydrogenation leads to 3,6-endopropylenetetrahydrophthalic acid (CCCLXVIII)[350]:



(CCCLXVII) (CCCLXVIII)

As a derivative of 1,3-cycloheptadiene, eucarvone (CCCLXIX) also undergoes normal diene synthesis with maleic anhydride[351]:



(CCCLXIX)

Recently Walter Reppe has added maleic anhydride, methyl acetylenedicarboxylate, quinones, and other dienophilic components to cyclooctatetrene (see page 507 ff.).

(4) COMPOUNDS WITH OXYGEN AS BRIDGE. (*a*) *Furans as Diene Components*; *Synthesis of Endoxo Compounds.* An extensive amount of data has been obtained, especially in the furan series, about the diene synthesis of cyclic compounds which have, in their ring systems, both a conjugated system and a hetero atom. The data present a rather well rounded picture of the chemical reactions which these compounds will undergo.

The system of conjugated double bonds of the furan system adds olefinic (and acetylenic) compounds in the 1,4 position to form a bicyclic ring with an oxygen atom as the bridge:

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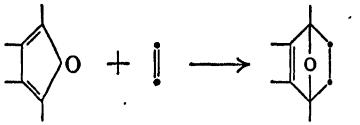
[350] Alder and Rickert, *Ber.*, **70**, 1354, 1366 (1937).

[351] Alder and Stein (*Ann.*, **515**, 167 (1935). West (*J. Chem. Soc.*, **1940**, 1162) who recently described the same adduct appears to have overlooked the first mentioned work.

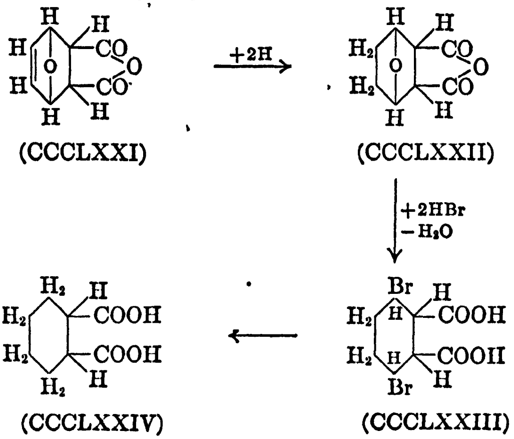


(CCCLXX)

The endoxo compounds of the type (CCCLXX) are all extremely labile and dissociate in solution. This dissociation depends more or less upon the substituents. In some cases it occurs at room temperature. Even in the solid phase the compounds often undergo the same dissociation at room temperature. If the compound is heated above its melting point, the dissociation is often complete, especially if the furan component is volatile.

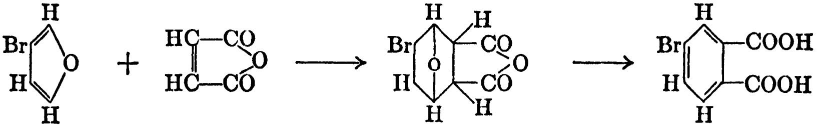
In the preparative application of the diene synthesis to the furan series, an important conclusion can be drawn from the behavior of the adduct; namely, that the use of higher temperatures (>100° to 120°C.) for accelerating the addition is out of the question. This limitation in the choice of reaction conditions is not serious, because these additions generally proceed rapidly at room temperature, and by using a solvent from which the adduct separates in solid form, a quantitative yield is obtained.

In spite of its unusual instability, it has been established beyond doubt that the adduct does not behave like a loose molecular complex. This may be shown in a variety of ways, many of which possess synthetic value. If the double bond in CCCLXX is saturated, a completely stable dihydro compound results whose oxygen bridge may be removed and replaced by hydrogen. The peripheral ring of CCCLXX appears in the form of a cyclohexane derivative. For example, the adduct (CCCLXXI) from furan and maleic anhydride can be hydrogenated to norcantharidine (CCCLXXII) which is converted through the intermediate product (CCCLXXIII) into hexahydrophthalic acid (CCCLXXIV)[193]:



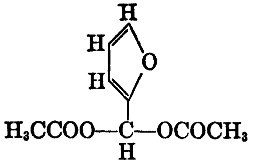
(CCCLXXI) (CCCLXXII) (CCCLXXIII) (CCCLXXIV)

The transformation into a benzene derivative is especially valuable as an indication of the structure of the furan adduct (CCCLXX). It has often been accomplished with the addition products of maleic anhydride.[352,353] The net result is equivalent to the elimination of water and the formation of a phthalic acid. This procedure can be illustrated by preparation of CCCLXXV, which is formed from β-bromofuran and maleic anhydride. It is converted by the above process into 4-bromophthalic acid (CCCLXXVI):

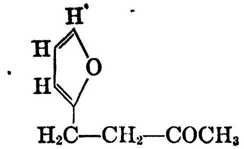


(CCCLXXV) (CCCLXXVI)

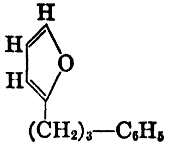
The formation of the endoxo compound as a normal diene synthesis on the double bond system of the furan nucleus confirms the correctness of the general scheme. It remains to indicate the scope of the reaction. This is extraordinarily broad in respect to the furan component, as shown by the large amount of experimental material. Among the many compounds investigated are furan[354] and its near homologues, α- and β-methylfuran,[354] α,α′-dimethylfuran,[354] and other derivatives of the same ring system, α- and β-bromofuran,[353] β-hydroxyfuran,[355] furfuryl methyl ether,[353] furfuryl acetate,[354] furfural diacetate (CCCLXXVII),[353] furfuryl acetone (CCCLXXVIII),[353] and α-furyl-γ-phenylpropane (CCCLXXIX)[356,357]:



(CCCLXXVII)



(CCCLXXVIII)



(CCCLXXIX)

An exception to the usual type of furan addition is to be found in the addition of 2-vinylfuran to maleic anhydride. The course of the reaction is represented in the accompanying structural diagram[358]:

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[352] Diels and Alder, *Ann.*, 490, 243 (1931).

[353] Van Campen and Johnson, *J. Am. Chem. Soc.*, 55, 430 (1933).

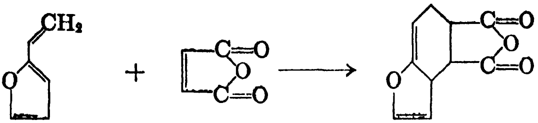
[354] Alder, (foot-note 1), "Die Methoden der Diensynthese," p. 3102.

[355] Hodgson and Davies, *J. Chem. Soc.*, 1939, 806.

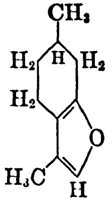
[356] Herz, *J. Am. Chem. Soc.*, 68, 2732 (1946).

[357] Pfau *et al.*, *Helv. Chim. Acta*, 18, 935 (1935). *Cf.* the similar furan component which Woodward [*J. Am. Chem. Soc.*, 62, 1478 (1940)] has employed in the diene synthesis.

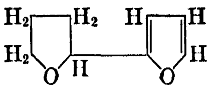
[358] Paul, *Bull. soc. chim.*, 10, 163 (1943); *Chem. Abstracts*, 38, 3978 (1944).



Even the more complex types, such as menthofuran (CCCLXXX)[359] and α-furyltetrahydrofuran (CCCLXXXI)[360] show a normal behavior with respect to the ease of formation and instability of the adducts:

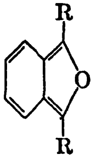


(CCCLXXX)



(CCCLXXXI)

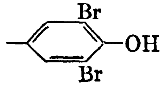
Likewise, the fusion of the furan system with a six-membered ring, which occurs in the isobenzofuran type (CCCLXXXII) does not diminish the additive tendency of the furan double bonds. There is an extensive amount of experimental data concerning the behavior of this series of compounds. Those which have been investigated up to the present are α,β-diphenyl-β,β′-benzofuran (CCCLXXXIIa),[148,361,362] α,α′-di-α-naphthyl-β, β′-benzofuran (CCCLXXXIIb),[363] and finally tetrabromophenolphthalidine (CCCLXXXIIc)[364,365]:



(a) R = C_6H_5

(b) R = α - $C_{16}H_7$

(c) R =



(CCCLXXXII)

As with the simple furans, the diene synthesis proceeds very smoothly with these bicyclic systems, and the resulting adducts dissociate easily into their components at low temperatures. The aromatization of these adducts (which proceeds with the elimination of water) is accomplished by the use of a hydrogen halide and proceeds with great ease. The synthesis of 1,4-diphenylnaphthalene-2-aldehyde from α,α-diphenyl-β,β'-benzofuran and acrolein[366] which can be carried out in one operation, serves as a good example:

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[359] Treibs, *Ber.*, **70**, 86 (1937).

[360] Kondo, Suzuki, and Takeda, *J. Pharm. Soc. Japan*, **55**, 142 (1935); *Chem. Zentr.*, **1935**,II, 2815; *Chem. Abstracts*, **29**, 7324 (1935).

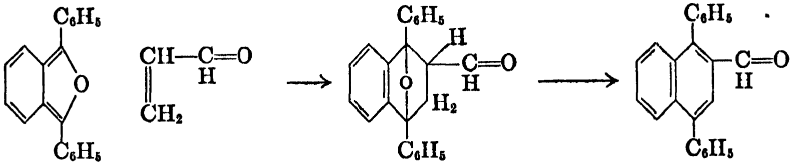
[361] Weiss and Abeles, *Monatsh.*, **61**, 162 (1932). Weiss and Beller, *ibid.*, **61**, 143 (1932).

[362] Barnett, *J. Chem. Soc.*, **1935**, 1326. Dufraisse and Priou, *Bull. soc. chim.*, **5**, 502 (1938). Bergmann, *J. Chem. Soc.*, **1938**, 1147.

[363] Weiss and Koltes, *Monatsh.*, **65**, 351 (1935).

[364] Weiss, *Monatsh.*, **71**, 6 (1938).

[365] Further diene syntheses with isobenzofuran derivatives; *cf.* Adams *et al.*, *J. Am. Chem. Soc.*, **62**, 56, 1233 (1940).



Other examples of the synthesis of the naphthalene system by this method have been given earlier (see pages 421 and 428).

Numerous experiments have shown that most furan derivatives are capable of undergoing the diene synthesis with the formation of an endoxo compound (CCCLXX). A few exceptions are known in which addition has not yet been achieved. These exceptions doubtless need reexamination and further investigation. The unreactive compounds include furans which carry such groups as —COOR, —C≡N, and —NO[353,367] on the ring,[368] α-hydroxyfuran[368] and α-phenyl-α'-(p-chlorophenyl)furan.[369]

The problem of suitable dienophiles must be solved before the applicability of the method to derivatives of furan can be properly gaged; *i.e.*, which olefin and acetylene derivatives can be employed for the synthesis of endoxo compounds (CCCLXX).

A number of compounds[370] are known which can add to complex furans of the type (CCCLXXXII; *i.e.*, quinone, α-naphthoquinone, maleic anhydride, acrolein, cinnamic ester, indene, and vinyl methyl ketone. Undoubtedly, many other unsaturated compounds could be used with satisfactory results.

The behavior of the simple monocyclic furans is somewhat different. Only the most active olefin and acetylene components, such as maleic anhydride and the esters of acetylenedicarboxylic acid, react with these furans. Moreover, no reaction is obtained with pyrocinchonic anhydride[193,371,372] or tetrolic ester,[352] thus indicating that the reaction is definitely limited in its scope.

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[366] Weiss and Abeles, *Monatsh.*, 61, 165 (1932).

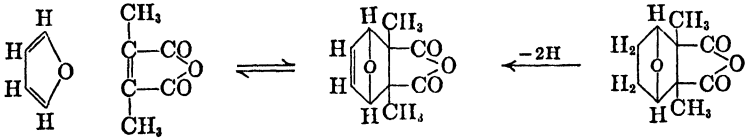
[367] Unfortunately a statement about the position of these groups on the furan nucleus is lacking. Van Campen, *Thesis*, Cornell University, shows them to be α-derivatives.

[368] Hodgsen and Davies, *J. Chem. Soc.*, 1939, 806. Compare the divergent behavior of β-hydroxyfuran described in the same work.

[369] Allen and Boyer, *Can. J. Research, Sect. A*, 9, 159 (1933); *Chem. Zentr.*, 1934,I 1474; *Chem. Abstracts*, 27, 5310 (1933).

[370] See the literature cited above.

These conditions have been investigated thoroughly in the case of the system furan + pyrocinchonic anhydride. The significance of the study of this addition lies in the fact that the expected adduct (CCCLXXXIII) should be converted by hydrogenation into the naturally occurring physiologically active cantharidin (CCCLXXXIV). The results of these experiments, which have been carried out under the most varied conditions, have been absolutely negative, obviously because the equilibrium, furan + pyrocinchonic anhydride ⇄ dehydrocantharidin (CCCLXXXIII), lies completely on the side of the cleavage products at the temperature necessary for addition:



(CCCLXXXIII) (CCCLXXXIV)

In confirmation of this conclusion, cantharidin is dissociated into furan and pyrocinchonic anhydride on dehydrogenation with palladium-charcoal, a process which presumably takes place through the intermediate dehydrocantharidin (CCCLXXXIII).[372,373] This observation furnishes valuable evidence for the structure of cantharidin.

The adducts of the furans with acetylenedicarboxylic ester or with the acid itself are especially important, since the doubly unsaturated primary product (CCCLXXXV) which arises in a normal manner may undergo a variety of reactions, many of which are of considerable synthetic value. The partial hydrogenation of the adducts leads to α,β-unsaturated carboxylic acids: *e.g.*, the adduct of furan and acetylenedicarboxylate (CCCLXXXV) on hydrogenation gives CCCLXXXVI. As derivatives of maleic acid, these may undergo further diene syntheses. Thus, a partially hydrogenated endoxonaphthalene derivative (CCCLXXXVII) is formed from the anhydride (CCCLXXXVI) and butadiene. The structure of this new adduct is similar to that of cantharidin (CCCLXXXIV)[374]:

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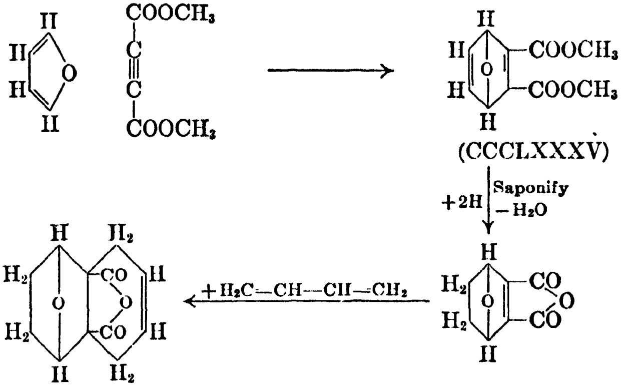
[371] Diels and Olsen, *J. prakt. Chem.*, 156, 285 (1940).

[372] Bruchhausen and Bersch, *Arch. Pharm.*, 266, 697 (1928).

[373] An indirect synthesis of cantharidin based on the diene synthesis has been presented on pp. 469–470.

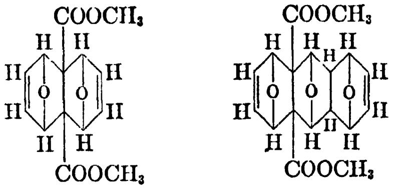
[374] Alder and Backendorf, *Ann.*, 535, 101 (1938).



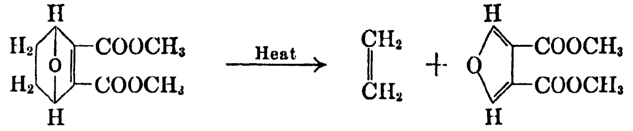
(CCCLXXXV)

(CCCLXXXVII) (CCCLXXXVI)

By heating acetylene dicarboxylate with an excess of furan, the primary addition product (CCCLXXXV) can undergo further diene synthesis with 1 or 2 moles of furan, to give compounds of a previously unknown type. These compounds belong to the hydrogenated naphthalene and anthracene series in which there are two and three endoxo bridges, respectively[371]:



Finally, the partially hydrogenated simple adducts from acetylenedicarboxylic ester and furan (CCCLXXXVIII) undergo a remarkable dissociation under the influence of heat with the formation of ethylene and furan-3,4-dicarboxylic ester (CCCLXXXIX)[375]:



(CCCLXXXVIII) (CCCLXXXIX)

Since this thermal decomposition proceeds so smoothly, the procedure possesses considerable preparative interest. Furan may be replaced by its derivatives, and the acetylenedicarboxylic ester by other acetylene compounds.[376]

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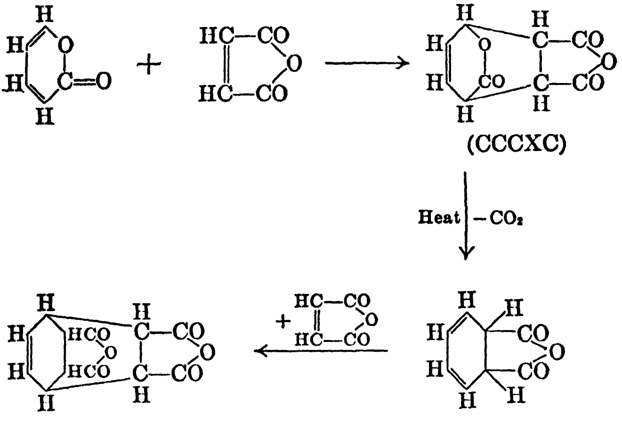
[375] Alder and Rickert, *Ber.*, **70**, 1354 (1937).

(*b*) *Cumalins* (*α-Pyrones*); *Behavior of α-Pyrone Systems in Diene Synthesis.* Like furan, cumalin (α-pyrone), another oxygen-containing heterocyclic compound, behaves normally in the diene synthesis; that is, the addition of a suitable olefin yields compounds with an —O—CO— bridge. However, maleic anhydride is the only olefinic compound which has been intensively investigated in this connection[377]:

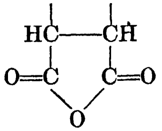


(CCCXC)

(CCCXCI)

CCCXCII)

A thorough study of the diene synthesis with cumalin and a few of its derivatives, like dimethylcumalin and isodehydroacetic ester has shown that the lactone bridge in the primary adduct (CCCXC) is readily eliminated as carbon dioxide. This dissociation occurs in a high boiling solvent and proceeds most smoothly when an excess of maleic anhydride is used. In this case, the —O—C=O bridge of the primary adduct is replaced by the group:



transforming the bicyclic heterocycle (CCCXC) into the carbocyclic bicyclo-[2.2.2]-octane (CCCXCII). It is possible that this transformation proceeds through the intermediate 1,3-cyclohexadiene (CCCXCI). In any event, the same dianhydride (CCCXCII) which is formed from cumalin by the addition of 2 moles of maleic anhydride and elimination of carbon dioxide[377] is also obtained from 1,2-dihydrophthalic anhydride (CCCXCI) and maleic anhydride (see page 469).

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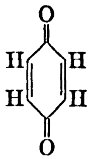
[376] *Cf.* the analogous thermal cleavage, which leads to the dicarboxylic esters of fulvene (see p. 465).

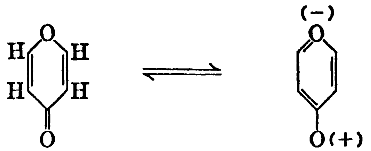
[377] Diels and Alder, *Ann.*, **490,** 257 (1931).

The cumalins usually are referred to as α-pyrones. At this point, therefore, it is fitting to consider briefly the experiments which have been carried out with the γ-pyrones (CCCXCIV). The two pyrone structures bear only a formal resemblance to each other, for the compounds differ widely in their chemical reactivity.

For example, the non-conjugated position of the double bonds in γ-pyrones should permit them to function as dienophiles in the diene synthesis. However, all attempts to bring about condensation with γ-pyrones have been unsuccessful. In this respect γ-pyrone differs fundamentally from *p*-quinone (CCCXCIII) to which it bears a structural resemblance:



(CCCXCIII)



(CCCXCIV) (CCCXCV)

The γ-pyrone type (CCCXCIV) also shows striking anomalies in numerous other reactions of its double bonds. These peculiarities recently have been attributed to an electromeric displacement of its bonds to the zwitterion form (CCCXCV).[378] It is probable that the behavior of γ-pyrone in the diene synthesis is due to this same effect. However, it is well to remember that many simple cyclic α,β-unsaturated ketones also show a diminished tendency to enter into the diene synthesis.[379]

2. Heterocyclic Ring Systems

The numerous diene syntheses previously described are, without exception, characterized by the fact that the six-membered ring resulting from the addition is *carbocyclic*. The material available for a discussion of the preparation of six-membered, *heterocyclic* rings is not so plentiful. Nevertheless, the method is sufficiently wide in scope to make possible a new synthesis of this type of compound.

A. Pyran and Chroman Series

The synthesis of this type of ring system depends upon the fact that α,β-unsaturated compounds, being conjugated systems, have the power to react with olefin and acetylene derivatives according to the following representation:

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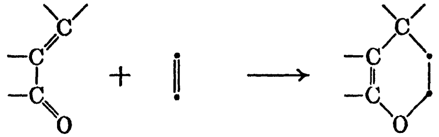
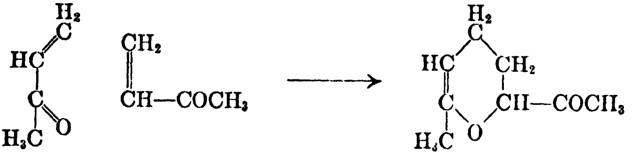
[378] *Eistert, Tautomerie und Mesomerie*, Enke, Stuttgart, 1938, p. 56 ff.

[379] *Cf.* for example, Robinson and Todd, *J. Chem. Soc.*, **1935,** 1530; Dane, Schmitt, and Rautenstrauch, *Ann.*, **532,**30 (1937); Winthrop Chem. Co. and Bockemüller, U. S. Patent, 2,179,809; Bartlett and Woods, *J. Am. Chem. Soc.*, **62,** 2933 (1940).

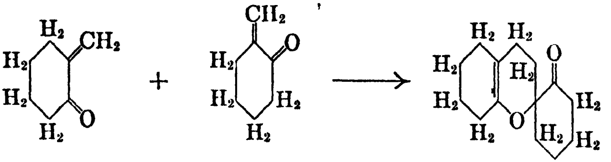


This reaction takes place with remarkable ease when α,β-unsaturated compounds possessing vinyl groups are heated. Acrolein, $CH_2{=}CH{-}CHO$,[380,381] methyl vinyl ketone, $CH_2{=}CH{-}CO{-}CH_3$,[382,383] ethyl vinyl ketone,[382] $CH_2{=}CH{-}COC_2H_5$, and phenyl vinyl ketone,[384] $CH_2{=}CH{-}CO{-}C_6H_5$, "dimerize" with the formation of pyran rings. In these instances the carbonyl oxygen of the olefin component which does not enter into the addition always occupies a position as near as possible to the oxygen of the ring. This is illustrated by the dimerization of methyl vinyl ketone to 2-acetyl-6-methyl-2,3-dihydropyran:

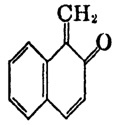


Since the monomer is converted easily into high polymers by a chain mechanism, it is advantageous to carry out the synthesis in the presence of "retarding agents" which repress this possible concurrent reaction.

The same transition takes place even more readily with more complex substances, such as *o*-methylenecyclohexanone (CCCXCVI)[385] and *o*-methylenequinones (quinone methides) (CCCXCVII).[386] These com-



(CCCXCVI)



(CCCXCVII)

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[380] Scherlin *et al.*, *J. Gen. Chem.* (*U. S. S. R.*), **8**, (70), 22 (1938); *Chem. Zentr.*, **1939,I**, 1971; *Chem. Abstracts*, **32**, 5398 (1938).

[381] Alder and Rüden, *Ber.*, **74**, 920 (1941).

[382] Merling, German Patent, 227,176; *Chem. Zentr.*, **1910,II**, 1421; *Chem. Abstracts*, **5**, 2154 (1911).

[383] Alder, Offermanns, and Rüden, *Ber.*, **74**, 905 (1941).

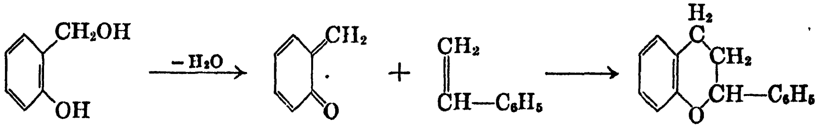
[384] Alder, Offermanns, and Rüden, *Ber.*, **74**, 926 (1941). Crotonaldehyde also forms a dimer, which is probably formed by the same mechanism (see also p. 396).

[385] Mannich, *Ber.*, **74**, 557, 565, 1007 (1941).

[386] Pummerer and Cherbuliez, *Ber.*, **52**, 1392 (1919). Fries and Brandes, *Ann.*, **542**, 48 (1939). Stuffmann, Dissertation, Braunschweig (1925).

pounds dimerize, as soon as they are formed, to pyran and chroman derivatives, respectively.

Another variation of the same procedure is apparent in the synthesis of pyran or chroman ring systems from *o*-hydroxybenzyl alcohols.[387] For example, saligenin (CCCXCVIII) and styrene when heated together yield 2-phenylchroman (CD). There can be little doubt that the reaction takes place through the intermediate, *o*-methylenequinone (CCCXCIX) and that a diene synthesis then takes place with the >C═C—C═O— system:

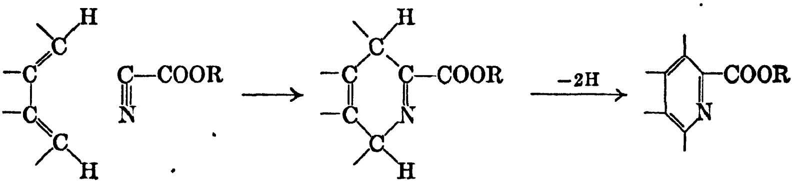


(CCCXCVIII) (CCCXCIX) (CD)

This method is generally applicable to the synthesis of chroman rings, for other methylol compounds can be substituted for saligenin, while styrene can be replaced by numerous other olefin and acetylene derivatives.[387,388]

B. Pyridine Series

Only a small amount of material is available on the application of the diene synthesis to the formation of pyridine nuclei. However, such nuclei are formed when suitable *N*-containing compounds function as dienophile components. The esters of cyanoformic acid, N≡C—COOR, are examples of such compounds. They add dienes to the C≡N— group and, without doubt, derivatives of 2,5-dihydropyridine (CDI) are formed primarily. Then, when hydrogen is present in the 2 and 5 positions, dehydrogenation to a pyridine derivative (CDII) takes place under the normal conditions of the reaction[389]:



(CDI) (CDII)

According to this procedure picolinic ester (CDIII) is obtained from cyanoformic ester and butadiene, while 2,3-dimethylbutadiene yields 4,5-dimethylpyridine-2-carboxylic ester (CDIV) by an analogous reaction:

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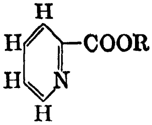
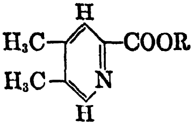
[387] Hultzsch, *J. prakt. Chem.*, **158**, 275 (1941).

[388] For the role of the diene synthesis in the resinification of phenol alcohols see Hultzsch, *Ber.*, **74**, 898 (1941).

[389] Unpublished observations.

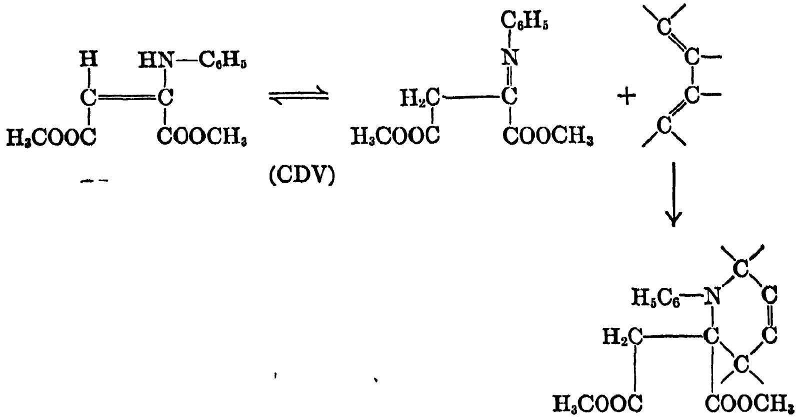


(CDIII)



(CDIV)

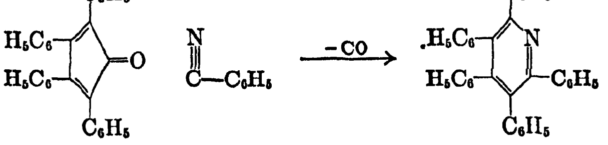
The synthesis of pyridine nuclei is also accomplished by the diene synthesis in a surprising manner by the use of derivatives of the esters of aminomaleic acid (CDV) as dienophile components. It has been shown that these compounds react in their tautomeric form, as derivatives of iminosuccinic acid, as long as the nitrogen atom still carries a hydrogen. The diene hydrocarbon does not add to the >C=C< group, but to the >C=N— double bond; this results in the formation of compounds of the Δ^3-piperidene series (CDVI)[390]:



(CDV)

(CDVI)

A third approach to the preparation of pyridine derivatives by the use of the diene synthesis starts with tetraphenylcyclopentadienone (CDVII). When treated with benzonitrile this ketone yields pentaphenylpyridine



(CDVII) (CDVIII)

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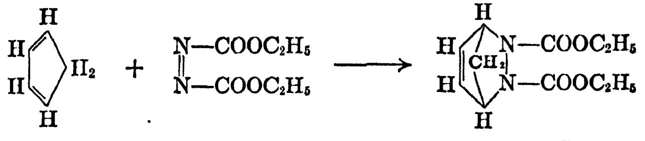
[390] Unpublished research.

(CDVIII)[391]; obviously, there is a simultaneous cleavage of carbon monoxide.

At present the available data in this field are insufficient to make a generalization possible.

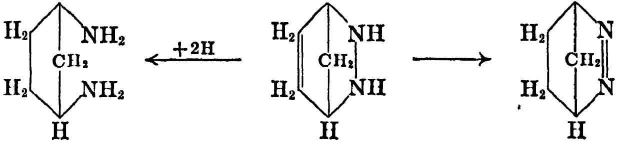
C. *o*-Diazine Series

The synthesis of *o*-diazine systems is accomplished very easily and smoothly, because the esters of azodicarboxylic acid, ROOC—N=N—COOR, are extremely reactive olefin components for the diene synthesis.[392,393] They combine spontaneously or at moderate temperatures with various dienes. Thus, cyclopentadiene and ethyl azodicarboxylate form *N,N'*-dicarbethoxyendomethylenetetrahydropyridazine (CDIX) in excellent yield, by merely mixing the components in ether solution.



(CDIX)

From the preparative view-point the adduct (CDIX) is significant, for a number of other products can be obtained from it. Saturation of the double bond and saponification of the ester groups followed by the loss of carbon dioxide give the alicyclic hydrazo compound (CDX) which can be converted to 1,3-diaminocyclopentane (CDXI) by energetic reduction, and to the cyclic azo compound (CDXII) by careful dehydrogenation:



(CDXI) (CDX) (CDXII)

These conversions, exemplified by the cyclopentadiene adduct, unquestionably possess great interest from the synthetic point of view. Many types are easily prepared in this manner, but others cannot be secured. Nevertheless, the addition of cyclopentadiene to azodicarboxylic ester, due to the great reactivity of the latter, lays the foundation for modifications in other directions. In place of cyclopentadiene, for example, aliphatic and aromatic alicyclic dienes, as well as compounds of the styrene series,[393] can be used, while the ester of azodicarboxylic acid can be substituted by its amide and other derivatives.

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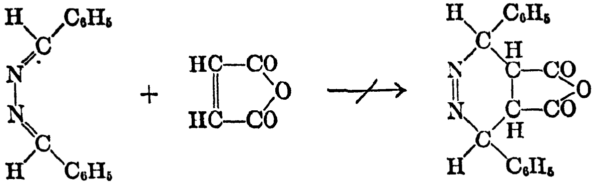
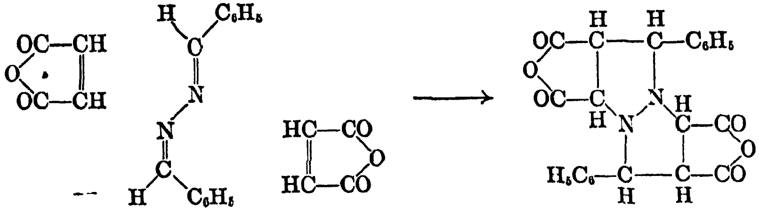
[391] Dilthey *et al.*, *Ber.*, **68**, 1162 (1935). *Cf.* also pp. 446–465.
[392] Diels, Blom, and Koll, *Ann.*, **443**, 242 (1925).
[393] Diels and Alder, *Ann.*, **450**, 237 (1926).

Some attempts to secure the *o*-diazine ring system with the aid of the diene synthesis have not led to the desired result. Thus, for example, benzalazine (CDXIII) and maleic anhydride or methyl maleate do not give the expected 1,4 addition; but 2 moles of anhydride react with 1 mole of azine, probably with 1,3 and 2,4 addition, and formation of a bis-pyrazolidine (CDXIV)[394]:



(CDXIII)

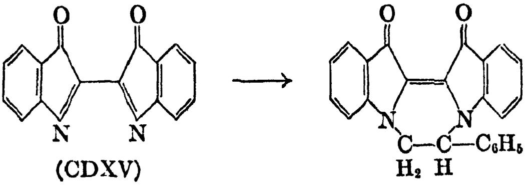


(CDXIV)

This assumption concerning the course of the addition places the process in parallel with the addition of cyanic acid, thiocyanic acid, and isocyanates to benzalazine.[395] However, exact experimental establishment of this is still lacking.

D. *p*-Diazine Series

In connection with the preparation of *p*-diazines by the diene synthesis, some recent studies on indigo have produced interesting results. De-



(CDXV)

+

$H_2C{=}CH{-}C_6H_5$

(CDXVI)

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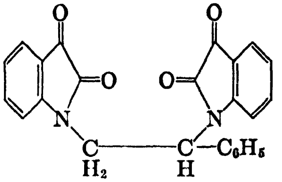
[394] Wagner-Jauregg, *Ber.*, 63, 3219 (1930).

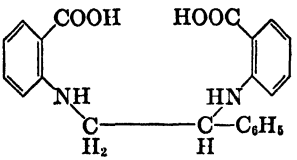
[395] Bailey *et al.*, *J. Am. Chem. Soc.*, 39, 279, 1322 (1917).

hydroindigo (CDXV) adds olefins of the type of styrene in the 1,4 position to the ends of the —N═C—C═N— system.[396]

Oxidative degradation of "styrene-indigo" (CDXVI) proceeds through the intermediate, "styrene-diisatin" (CDXVII), to "styrene-dianthranilic acid" (CDXVIII), thus proving that the original addition is 1,4:



(CDXVII)



(CDXVIII)

This reaction can be varied considerably with respect to the olefin component. Thus it has been shown that styrene can be substituted by a series of similarly constituted addends, such as anethol, isoeugenol, safrole, and isosafrole.[397] It is remarkable that dienophiles like maleic anhydride and quinone which, in all other cases have been superior, fail to react in this instance.

III. CYCLOOCTATETRENE IN DIENE SYNTHESIS

Cyclooctatetrene was first synthesized and its properties reported by Willstätter.[398] Some doubt concerning the structure of his compound was entertained, however, because its properties were so similar to those of styrene,[399] with which cyclooctatetrene is isomeric. Recent work by Reppe[400] has fully confirmed that of Willstätter and thrown more light on the chemistry of this interesting compound.[401] It is conveniently prepared in excellent yield by polymerizing acetylene in the presence of a nickel catalyst' (nickel cyanide, nickel thiocyanate, nickel acetoacetic ester). The reaction is carried out in tetrahydrofuran at 60° to 70°C. and at a pressure of more than 20 atmospheres.[400] Ethylene oxide facilitates the reaction. The hydrocarbon is a golden-yellow liquid with a boiling point of 142° to 143°C. at 760 mm., 42° to 42.5°C. at 17 mm. It does not resemble benzene in its reactions but acts like an unsaturated, aliphatic hydrocarbon. On hydrogenation it absorbs 3 moles of H rapidly and a fourth more slowly. It adds 3 but not 4 moles of Cl or Br and the hexahalide does not absorb H. Alkaline hypochlorite oxidizes it to terephthalaldehyde. Cyclooctatetrene dimerizes and can undergo the diene synthesis.

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[396] Pummerer and Fiesselmann, *Ann.*, **544,** 206 (1940).

[397] Pummerer and Stieglitz, *Ber.*, **75,** 1072 (1942).

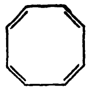
[398] Willstätter and Waser, *Ber.*, **44,** 3423 (1911). Willstätter and Heidelberger, *Ber.*, **46,** 517 (1913).

[399] For a review on cyclooctatetrene in which the earlier references are given see Baker, *J. Chem. Soc.*, **1945,** 258.

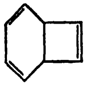
[400] Reppe, American Intelligence Division Report No. 4149 PB 1112; British Chemical Sub-committee Reports Nos. 5937-45 and R6288-45.

[401] Recently Cope and Overberger (*J. Am. Chem. Soc.*, **69,** 976 (1947); *ibid.*, *in press*) have completely substantiated Willstätter's work and proved that the compound synthesized from pseudopelletierine is identical with cyclooctatrene prepared from acetylene.

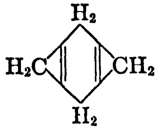
Because of the variety of reactions indicated above, cyclooctatetrene has been represented by formulas CDXIX, CDXX, and CDXXI. It



(CDXIX)



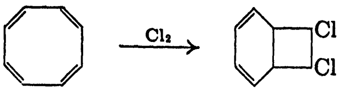
(CDXX)



(CDXXI)

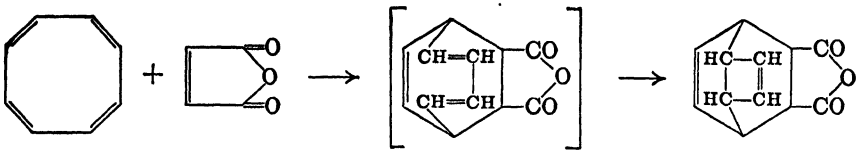
should not be concluded, however, that these formulas represent various tautomeric forms of the hydrocarbon. On the contrary, physical measurements (Raman spectrum,[402] infra-red spectrum) indicate that CDXIX is the correct structure. The other formulas are advanced to explain certain reactions of the compound and addition products of CDXIX may give products with the skeleton of CDXX or CDXXI, by rearrangement of the bond system in the addition product.

For example, addition of 1 mole of Cl to cyclooctatetrene gives a dichloro compound, the structure of which has been shown to be CDXXII:



(CDXXII)

The same type of reaction takes place when dienophiles such as maleic anhydride are added to the hydrocarbon. Temperatures of at least 100°C. are necessary and the products always absorb 1 mole of hydrogen less than would be expected of a normal adduct. This latter fact and the observation that the elements of cyclobutene are eliminated from the quinone adduct on pyrolysis indicate that a secondary reaction has taken place. Therefore the following mechanism in which maleic anhydride acts as the dienophile may be suggested:



(CDXXIII)

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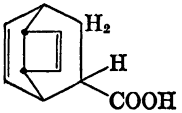
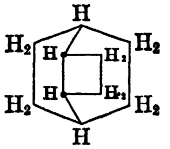
[402] Lippincott and Lord, *J. Am. Chem. Soc.*, 68, 1868 (1946).

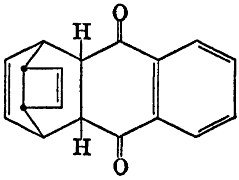
A second mole of maleic anhydride will not add. Acrylic acid, quinone, and naphthoquinone have been added to give compounds CDXXIV, CDXXV, and CDXXVI, respectively:



(CDXXIV)

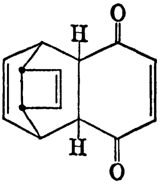


(CDXXVII)

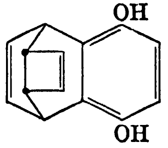


(CDXXVI)

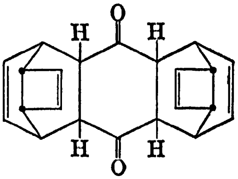
The acrylic acid adduct (CDXXIV) has been hydrogenated and decomposed through the azide and amine to a saturated tricyclic hydrocarbon (CDXXVII). The quinone adduct is obtained in two forms, a quinonoid CDXXV and a benzenoid CDXXVIII, depending upon the reaction temperature; CDXXV can also be converted to CDXXVIII by heat:



(CDXXV)



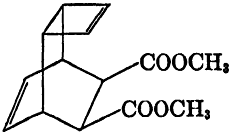
(CDXXVIII)



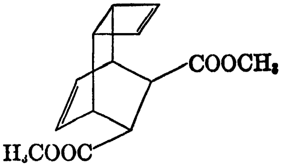
(CDXXIX)

A second mole of dienophile will not add but quinone will add 2 moles of the hydrocarbon to give the product CDXXIX.

The adduct (CDXXIII) has been reduced stepwise and various esters of it and of the reduction products have been prepared. The *cis*-dimethyl ester CDXXX has been converted to the *trans*-dimethyl ester CDXXXI by the action of dilute sodium methoxide, a reaction typical of tetrahydrophthalic esters:

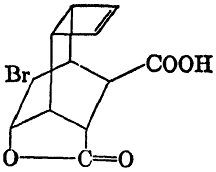


(CDXXX)



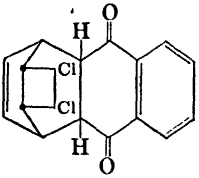
(CDXXXI)

When bromine in methanol is allowed to react on the potassium salt of 3,6-endocyclobutadienylenecyclohexene-1,2-dicarboxylic acid (CDXXX or CDXXXI; $CH_3 = K$; the *cis* or *trans* form is not specified) a bromolactone acid CDXXXII is obtained.

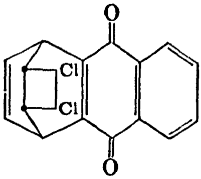


(CDXXXII)

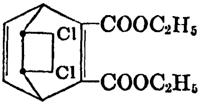
It will be noted that the cyclooctatetrene addition product with chlorine (CDXXII) is still a diene. As such, it adds dienophiles in much the same manner as cyclohexadiene. Both 1,4-naphthoquinone and ethyl acetylenedicarboxylate react with CDXXII to give adducts that may be represented by CDXXXIII and CDXXXV, respectively:



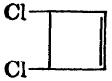
(CDXXXIII)



(CDXXXIV)



(CDXXXV)



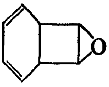
(CDXXXVI)

CDXXXIII melts at 221°C., turns red in alkali, and is oxidized by air therein to CDXXXIV. The latter gives anthroquinone when heated to 180°C. The other product of this pyrolysis is 2,3-dichlorocyclobutene (CDXXXVI), a low melting solid (44°C.) which boils at 130°C. at 760 mm. The adduct from ethyl acetylenedicarboxylate reacts in a similar manner.

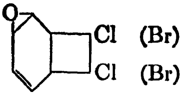
The isolation and identification of 2,3-dichlorocyclobutene, the fact that a bicyclooctane derivative has been obtained, and the observation that the dichloride (CDXXII) gives a diacetate which can be hydrogenated, saponified to the glycol, and oxidized to hexahydrophthalic acid (thus showing the ortho fusion of the rings) establishes the structure of the dichloro derivative of the hydrocarbon.

Dibromocyclobutene has been prepared from the adduct of the dibromide of cyclooctatetrene and ethyl acetylenedicarboxylate by a similar procedure.

Cyclooctatetrene as well as the dichloro and dibromo derivatives give oxides when treated with perphthalic and perbenzoic acid, respectively. These compounds may be represented by CDXXXVII and CDXXXVIII:

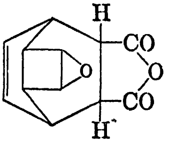


(CDXXXVII)

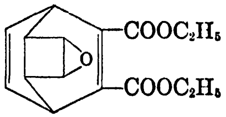


(CDXXXVIII)

As a diene CDXXXVII will add maleic anhydride or ethyl acetylenedicarboxylate to give the compounds CDXXXIX and CDXL; the double bonds in these products may be reduced without affecting the oxide linkage:



(CDXXXIX)



(CDXL)

Cyclooctatetrene dimerizes slowly at room temperature and more rapidly by heating to give two products, one melting at 43°C., the other an oil boiling at 297°C. The dimerization is presumably a diene synthesis. The dichloro compound dimerizes in the presence of acetic acid to a compound melting at 190°C. It depolymerizes on standing or warming. The dibromo derivative reacts in the same manner in chlorobenzene.

This brief summary of cyclooctatetrene indicates the great variety of reactions that the hydrocarbon will undergo. The data are necessarily incomplete but serve to point out the types of reactions that can be expected in the diene synthesis. Doubtless more details will be available in the near future, and since the cost of the compound is expected to be low, it will probably be produced on a large scale and find application in many fields.

Syntheses with Diazomethane

By BERND EISTERT

Translated and revised by Fred W. Spangler

I. INTRODUCTION

Diazomethane is known to every organic chemist as a methylating agent for acidic compounds such as carboxylic acids, phenols, and enols. It transforms these compounds into their methyl esters or ethers, respectively. It has a great advantage over other methylating agents in that it can be employed in a neutral medium and that it yields no non-volatile by-products.

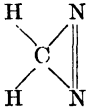
Besides this known reaction of diazomethane, there have appeared more recently other series of reactions. These, in part, are new and are so useful today in obtaining compounds of importance conveniently and inexpensively, that it is worth while to consider their relationship and to point out their capability of application. Among these reactions are those which have become important from the preparative standpoint and those whose significance lies more in the analytical field in which they have been applied to problems of constitution.

The following discussion will deal chiefly with diazomethane itself, although occasionally it will refer also to the behavior of its homologues and substitution products.

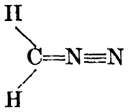
Before we turn to the various reactions separately, our attention should be focused briefly on the constitution of diazomethane, which indeed is responsible for its behavior.

II. CONSTITUTION OF DIAZOMETHANE

According to the classical structural theory, two formulas for the compound of elementary composition CH_2N_2 have come into consideration, the three-membered ring I and the open structure II. There is consider-



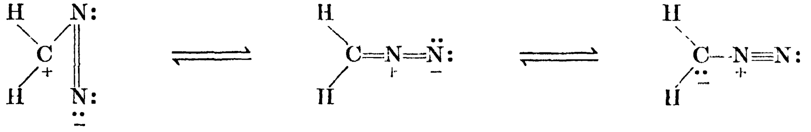
(I)



(II)

able basis (Curtius[1] and Thiele[2]) for both formulas and a choice between them does not appear possible. Recently Boersch,[3] in electron diffraction studies, pointed out that both the nitrogen atoms and the carbon atom in diazomethane vapor must lie in a straight line. According to this, formula I appears to be disproved, but the electronic theory leads us to the conclusion that both formulas are right.[4]

A classical structural formula, as is known, is a combination of atoms connected by straight lines. The kinds of valences are not indicated. According to the electronic theory two distinct types of valence are possible: a real binding caused by the mutual sharing of an electron pair (covalence); and a purely electrostatic ionic relation as in Na^+Cl^- (electrovalence). The nitrogen atom can exhibit only four real bonds, the so called fifth valence being an ionic relation. From this standpoint classical formula II of diazomethane now becomes electronic formula IV or V, depending upon whether one of the five valences of the middle nitrogen atom is carried to the carbon atom or to the other nitrogen atom as an ionic relation. In formula I it can be considered that only one carbon-nitrogen valence is a real bond, the other being an ionic relation. Formula I thus becomes, after the shift of an electron pair, electronic formula III or V, depending upon whether the carbon atom becomes the center of a positive or negative ionic charge.



(III) (IV) (V)

In the consideration of a formula it should be kept in mind that the three electronic formulas (III, IV, and V) differ only in the arrangement of the electrons and not in the arrangement of the atoms. Also, formula III fulfils the requirement that both nitrogen atoms and the carbon atom are able to lie in a straight line. According to present theory, formulas distinguished from one another only through the distribution of electrons are extreme formulas of a mesomeric system.[4] The extreme formulas III, IV, and V thus describe the homogeneous compound diazomethane, the behavior of which should be accounted for on the basis of one or more of the mesomeric forms. The extreme formulas have the significance of reaction formulas. Formula V, especially, appears later in reactions.

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[1] Curtius, *J. prakt. Chem.*, **39**, 107 (1889).

[2] Thiele, *Ber.*, **44**, 2522 (1911).

[3] Boersch, *Monatsh.*, **65**, 331 (1935).

[4] *Cf.* Eistert, *Tautomerie und Mesomerie*, Enke, Stuttgart, 1938; Müller, *Neuere Anschauungen der organischen Chemie*, Springer, Berlin, 1940; Pauling, *The Nature of the Chemical Bond*, 2nd ed., Cornell University Press, Ithaca, 1940; Remick, *Electronic Interpretations of Organic Chemistry*, Wiley, New York, 1943; Watson, *Modern Theories of Organic Chemistry*, 2nd ed., Clarendon Press, Oxford, 1941; Wheland, *The Theory of Resonance and Its Application to Organic Chemistry*, Wiley, New York, 1944.

III. PREPARATION

For the preparation of diazomethane the following methods come into consideration.

(1) SYNTHESIS FROM CHLOROFORM AND HYDRAZINE.[5] According to

$$CHCl_3 + H_2NNH_2 + 3KOH \longrightarrow CH_2N_2 + 3KCl + 3H_2O$$

this method one obtains gaseous diazomethane, which for many purposes is as useful as the diazomethane solution obtained by the saponification method.

(2) ALKALINE SAPONIFICATION OF COMPOUNDS OF GENERAL FORMULA R—N(CH$_3$)NO, IN WHICH R REPRESENTS A GROUP EASILY SPLIT OFF BY ALKALI, SUCH AS AN ACYL GROUP. The best known examples belonging to this method are the saponification of nitrosomethylurethan (R equals $COOC_2H_5$) with alcoholic potassium hydroxide according to von Pechmann[6] and of nitrosomethylurea (R equals $CONH_2$) with aqueous alkali according to Werner[7] and Arndt and Amende[8]:

$$CH_3N(NO)COOC_2H_5 + 2KOH \longrightarrow CH_2N_2 + K_2CO_3 + C_2H_5OH + H_2O$$

$$CH_3N(NO)CONH_2 + KOH \longrightarrow CH_2N_2 + KCNO + 2H_2O$$

Diazomethane has also been obtained by the saponification of nitrosomethylbenzamide[6] and of methyl-*p*-nitrophenylnitrosamine.[9]

In the saponification procedures the starting materials generally used, nitrosomethylurea or nitrosomethylurethan, have advantages as well as disadvantages. Nitrosomethylurea (a solid) is very easily prepared and has no irritating effect. It can be kept in storage only in the cold. At temperatures in the neighborhood of 30°C. it may undergo decomposition with the formation of methyl isocyanate, nitrogen, and water. At about 20° the decomposition in the course of several months becomes appreciable, there being formed in place of methyl isocyanate its trimer, *N*-trimethylcyanuric acid.[10] Nitrosomethylurethan (a liquid) has a strongly irritating effect especially on the mucous membranes and is not convenient to prepare. It is considered harmless and capable of storage, but occasionally, after standing for several years, it decomposes spontaneously.[11] It is recommended, therefore, that nitrosoalkyl compounds always be kept at a temperature below 20° in the dark and in a bottle which is as alkali-free as possible.

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[5] Staudinger and Kupfer, *Ber.*, **45**, 501 (1912).

[6] von Pechmann, *Ber.*, **27**, 1888 (1894); **28**, 855 (1895).

[7] Werner, *J. Chem. Soc.*, **115**, 1098 (1919).

[8] Arndt and Amende, *Angew. Chem.*, **43**, 444 (1930). Arndt and Scholz, *ibid.*, **46**, 47 (1933).

[9] Noelting, cited in Bamberger and Müller, *Ber.*, **33**, 101 (1900).

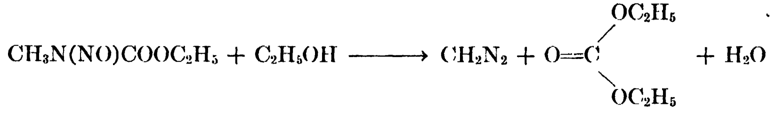
[10] Arndt, Loewe, and Avan, *Ber.*, **73**, 606 (1940).

All such nitrosomethylamino compounds undergo explosive decomposition when, in an undiluted state, they come in contact with strong alkali. In the production of diazo compounds, therefore, care must be taken that the heat of the reaction is carried away by sufficient solvent. Efficient stirring and external cooling may also be advantageous (if a glass stirrer is used, take care; see page 518).

In the preparation of a diazomethane solution the starting material usually employed is the inexpensive nitrosomethylurea.[8,10] This method is convenient because distillation is not necessary in experiments on a small scale. In larger runs distillation may be carried out to produce more concentrated diazomethane solutions (as in the preparation from nitrosomethylurethan) which are free of methanol and can easily be freed of traces of water.

Since compounds containing hydroxyl groups often have a considerable catalytic influence on many reactions of diazomethane, their presence may be desirable under certain circumstances. Nitrosomethylurethan is generally employed as the starting material in such cases. Its ether solution is mixed with methanolic potassium hydroxide and carefully distilled. The distillate contains diazomethane, ether, and methanol. Care must be taken to avoid too rapid heating; otherwise the nitroso compound may become concentrated before it is completely decomposed and the action of the alkali on it may cause a violent explosion. In a modification of the nitrosomethylurethan saponification, gaseous diazomethane is obtained by the reaction of the nitroso compound with a dilute solution of sodium in ethylene glycol.[12]

Less known, perhaps, is the reaction of nitrosomethylurethan in alcoholic solution in the presence of catalytic amounts of alkali carbonate in which the products formed are diazomethane and diethyl carbonate[13]:



$$CH_3N(NO)COOC_2H_5 + C_2H_5OH \longrightarrow CH_2N_2 + O{=}C\begin{matrix}\diagup OC_2H_5\\ \diagdown OC_2H_5\end{matrix} + H_2O$$

This permits the use of diazomethane in a nascent state in a neutral medium. Nitrosomethylurethan is added dropwise to an alcoholic solution of the reacting compound containing some potassium carbonate at such a rate that the diazomethane which is formed reacts immediately and no undesired concentration is reached. According to this method, however, only those reactions can be carried out which take place in the presence of compounds containing hydroxyl groups. Other *N*-nitrosoalkylamino compounds can be employed in a similar manner for the preparation of nascent diazomethane.

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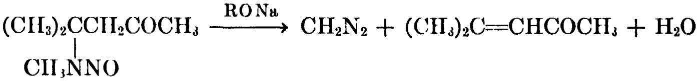
[11] *Cf.* Weygand, *Organisch-chemische Experimentierkunst*, Voss, Leipzig, 1938, p. 9.
[12] Meerwein and Burneleit, *Ber.*, **61**, 1845 (1928).
[13] Meerwein, German Patent, 579,309; *Chem. Abstracts*, **27**, 4546 (1933).

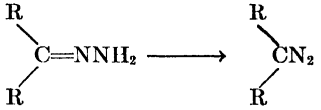
More recently the preparation of diazomethane and its homologues from nitroso-β-alkylaminoisobutyl methyl ketones has found increasing use[14]:



$$\underset{\mathrm{CH_3NNO}}{(\mathrm{CH_3})_2\mathrm{C}}\mathrm{CH_2COCH_3} \xrightarrow{\mathrm{RONa}} \mathrm{CH_2N_2} + (\mathrm{CH_3})_2\mathrm{C{=}CHCOCH_3} + \mathrm{H_2O}$$

This method affords very good yields and inexpensive starting materials are employed. The stability of the nitrosoamino ketones in storage is much better than the nitroso compounds mentioned previously.

Disubstituted diazomethanes can be obtained by the oxidation of hydrazones of ketones[15]:



Diazoacetic ester is formed by diazotizing the ethyl ester of glycine[16]:

$$\mathrm{C_2H_5OOCCH_2NH_2} + \mathrm{HNO_2} \longrightarrow \mathrm{C_2H_5OOCCHN_2} + 2\mathrm{H_2O}$$

IV. PROPERTIES

Diazomethane is a highly toxic, yellow gas. It has a boiling point of −23°C. and a melting point of −145°C. In work requiring its continued use there is danger of developing a sensitivity to attacks of asthma. Individuals differ greatly in their susceptibility. With reasonable care, however, no difficulty should be encountered in handling an occasional small quantity.

The explosiveness of diazomethane is generally overestimated. In dilute solution in the cold it is fairly safe. Undiluted liquid diazomethane and concentrated solutions on the other hand can explode violently, especially if impurities are present. Gaseous diazomethane, even on dilution with nitrogen, likewise may undergo explosive decomposition, especially at a temperature of 100°C. or higher. It has been pointed out[17] that explosions of gaseous diazomethane are caused repeatedly by rough glass surfaces. The use of ground glass apparatus, therefore, is not recommended in working with diazomethane. Also to be avoided as much as possible is the use of a glass stirrer within a glass sleeve where the grinding action can produce glass dust and rough surfaces. Most accidents in the work with diazomethane, however, are not caused by the diazomethane itself, but rather by the reaction of undiluted nitroso compounds with strong alkali, as is possible in the preparation according to von Pechmann.[6] Explosive intermediate products sometimes also appear in the reactions of diazomethane (see "Experimental Procedures," page 566).

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[14] Adamson and Kenner, *J. Chem. Soc.*, **1935**, 286; **1937**, 1551; **1939**, 181.

[15] Curtius and Thun, *J. prakt. Chem.*, **44**, 161 (1891). Curtius and Rauterberg, *ibid.*, **44**, 192 (1891). Curtius and Pflug, *ibid.*, **44**, 535 (1891). Curtius and Lang, *ibid.*, **44**, 544 (1891).

[16] Curtius, *Ber.*, **16**, 2230 (1883).

Solutions of diazomethane in ether or dioxane decompose only slowly at low temperatures. Decomposition is more rapid if alcohols or water are present. Reactions of diazomethane with acidic compounds appear later. It is more stable toward alkali. On the other hand, alkali metals produce explosions with diazomethane. Copper powder causes active decomposition with the evolution of nitrogen and the formation of insoluble white flakes of polymethylene, $(CH_2)_x$. Solid calcium chloride or a small boiling stone produces the same result. This boiling stone effect[18] always occurs during the action of diazomethane solutions on solid substances, at least as a side reaction.

V. REACTIONS WITH ACIDIC HYDROGEN

As mentioned earlier, the reaction of diazomethane with a compound X—H, which contains a sufficiently acidic hydrogen atom, proceeds according to the following scheme:

$$X{-}H + CH_2N_2 \longrightarrow \underset{\text{(VI)}}{X{-}H{\leftarrow}CH_2N_2} \longrightarrow \underset{\text{(VII)}}{CH_3N_2^{+}X^{-}} \longrightarrow CH_3X + N_2$$

The effective reaction formula of diazomethane in this case is the extreme formula V. The hydrogen bridge VI is first formed by the movable proton of compound X—H and the lone electron pair of the carbon atom of diazomethane. Subsequent dissociation leads to the formation of the diazonium salt VII. This loses nitrogen and the anion X combines with the methyl cation to form the compound CH_3X.

This scheme explains why diazomethane reacts instantly with a movable hydrogen atom and is transformed into a methyl group. It is readily apparent that diazomethane can be used to determine the presence of movable hydrogen atoms. This has been especially important in work with tautomeric compounds. Of course, certain factors have to be taken into consideration.[19]

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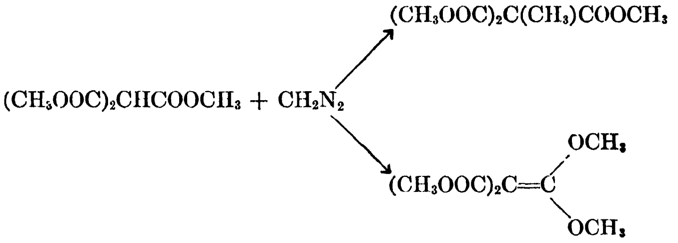
[17] Meerwein, private communication.

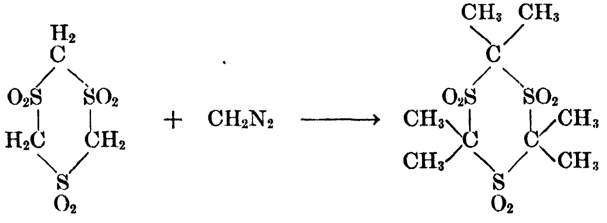
[18] Arndt, Amende, and Ender, *Monatsh.*, **59**, 218 (1932).

If a keto-enol equilibrium is present and diazomethane yields the enol ether exclusively, the enol form is more acidic than the accompanying keto form and is preferentially methylated. Even if the enol form is present only in small amount, the enol ether is formed exclusively as the equilibrium shifts in its favor. The enol ether can also result by way of the reaction of the carbonyl group (see "Indirect Methylation," page 535).

If, on the other hand, the *C*-methyl derivative is formed, the C—H form as such is acidic enough to react with diazomethane. Such compounds which can enolize form *C*- and *O*-methyl derivatives side by side. Thus trimethyl methanetricarboxylate yields trimethyl ethane-1,1,1-tricarboxylate and the derivative of the enol form, the dimethyl ketenedimethylacetaldicarboxylate.[20] It can be shown that the *C*-methyl derivative is not formed by rearrangement of the enol ether.



Finally, if the *C*-methyl derivative is formed exclusively, the compound is not able to enolize. Thus trimethylene trisulfone with diazomethane yields exclusively a product twice methylated at each carbon atom. This is evidence, therefore, that the sulfomethylene group, contrary to the classical conception, does not enolize.[20]



Cyanuric acid also does not enolize, for it yields with diazomethane the *N*-methyl derivative exclusively[21]:

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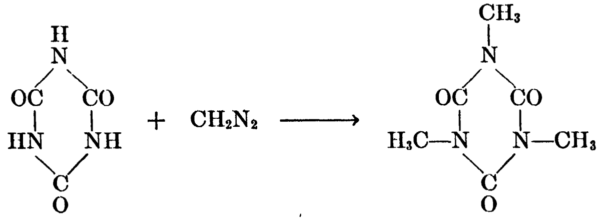
[19] Arndt, *Rev. faculté sci. univ. Istanbul*, **1**, No. 4, 7 (1936).
[20] Arndt and Martius, *Ann.*, **499**, 247, 268, 274 (1932).
[21] Palazzo and Scelsi, *Gazz. chim. ital.*, **38 I**, 664 (1908).



Although enolization of the amide group is, in general, very rare, a few exceptions have appeared.[22] Diazomethane has been very useful in helping to clear up the structures of these compounds.

Hydrocyanic acid reacts with diazomethane with the formation of acetonitrile and methyl isocyanide[23]:

$$HCN + CH_2N_2 \longrightarrow CH_3CN \text{ and } CH_3NC$$

The trisulfonylmethane $(RSO_2)_3CH$, which is strongly acidic in aqueous solution, is methylated by diazomethane, in agreement with the theory,[24] at the carbon atom.[25]

Contrary to wide-spread opinion, alcoholic hydroxyl groups also can be methylated by diazomethane if acidifying groups, such as the COOR group, are adjacent.[26] Thus the hydroxyl groups of tartronic and mesotartaric acids and their esters are methylated smoothly.

Weakly acidic compounds are not readily methylated in ethereal solution because of the neutralizing effect of the solvent. For example, trichloroethanol does not react with diazomethane in ethereal solution, but is converted smoothly to its methyl ether in heptane solution.[27] In order to suppress possible undesired side reactions of hydroxyl groups, therefore, diazomethane is always used in an ethereal solution.

It has been shown[28] that methylation (and many addition) reactions of diazomethane are accelerated catalytically by water or alcohol. For example, glycine does not react with diazomethane in absolute ether. However, after the addition of some water or methanol, a vigorous reaction takes place with the formation of betaine[28]:

$$H_2NCH_2COOH + CH_2N_2 \longrightarrow (CH_3)_3\overset{+}{N}CH_2CO\overset{-}{O}$$

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[22] *Cf.* Arndt and Eistert, *Ber.*, **71**, 2040 (1938). Biltz, *ibid.*, **72**, 807 (1939).

[23] von Pechmann, *Ber.*, **28**, 857 (1895). Peratoner and Palazzo, *Gazz. chim. ital.*, **38 I**, 102 (1908).

[24] *Cf.* Arndt and Eistert, *Ber.*, **74**, 423, 427, 432 (1941).

[25] Böhme and Marx, *Ber.*, **74**, 1667 (1941).

[26] Schmidt, private communication. *Cf.* Merkel, Dissertation, Heidelberg, 1940. Schmidt and Zeiser, *Ber.*, **67**, 2120, 2127 (1934).

[27] Meerwein, Bersin, and Burneleit, *Ber.*, **62**, 1006 (1929).

[28] Biltz and Paetzold, *Ber.*, **55**, 1069 (1922).

Certain aldoximes have been shown to react with diazomethane with the formation of both *O*- and *N*-methyl ethers.[29] The reaction is of value because it makes possible the synthesis of rarely occurring isomeric pairs of *N*-methyl ethers of aldoximes.

It is interesting to note that diazomethane reacts with ammonium or amine salts of organic or inorganic acids to form the corresponding methyl esters.[30] Ammonia or the corresponding amine is evolved. Thus, ammonium propionate and ammonium chloride react with diazomethane to give methyl propionate and methyl chloride, respectively.

The methyl esterification of easily lactonized hydroxy acids is conveniently carried out with diazomethane. Whereas the usual methods of esterification are not readily applicable, diazomethane smoothly converts γ-hydroxy-γ-(*p*-methoxyphenyl)butyric acid to its methyl ester.[31]

VI. REACTIONS WITH CARBONYL COMPOUNDS

1. Aldehydes

Meyer[32] was the first to observe that diazomethane also reacts with aldehydes with the evolution of nitrogen. Benzaldehyde and heptaldehyde were shown by Schlotterbeck[33] to yield the corresponding methyl ketones. Schlotterbeck concluded that this was a general reaction of aldehydes in which the hydrogen atom of the aldehyde group was sufficiently movable (as in the acidic compounds mentioned previously) for methylation to take place.

This, of course, is not in agreement with our present knowledge, according to which the aldehyde hydrogen atom is not acidic but is capable of being removed only as a hydrogen atom, or even as a hydrogen anion.[1] Schlotterbeck also found some cases[34] in which the products obtained from aldehydes and diazomethane had other properties than the corresponding methyl ketones, which had been assigned their structures on the basis of their syntheses by other means. For example, he believed that chloral and diazomethane yielded 1,1,1-trichloroacetone. Since the product exhibited wholly different properties than those described by Blaise[35] for trichloroacetone, he assumed that Blaise had another or an impure product. Actually, however, Blaise's data were proved[36] to be correct and Schlotterbeck's product was found to have a different structure.

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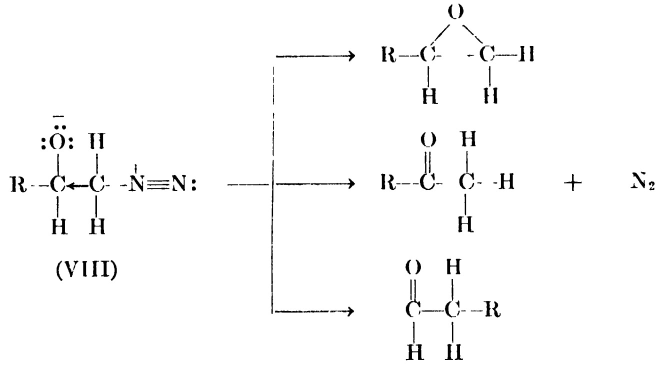
[29] Thompson and Baer, *J. Am. Chem. Soc.*, **62**, 2094 (1940).
[30] Frankel and Katchalski, *J. Am. Chem. Soc.*, **65**, 1670 (1943); **66**, 763 (1944).
[31] Soffer and Hunt, *J. Am. Chem. Soc.*, **67**, 692 (1945).
[32] Meyer, *Monatsh.*, **26**, 1300 (1905).
[33] Schlotterbeck, *Ber.*, **40**, 479 (1907).
[34] Schlotterbeck, *Ber.*, **42**, 2559 (1909).
[35] Blaise, *Bull. soc. chim.*, **15**, 736 (1914).
[36] Arndt, Amende, and Ender ,*Monatsh.* **59**, 214 (1932).

Although the reaction between diazomethane and aldehydes and its dependence on the structures of the aldehydes is now clear (see below), until recently a great deal of erroneous data are found in the literature on the products resulting from this reaction. While some of this has been due to the acceptance of the conclusions of Schlotterbeck without further evidence, the fault probably lies also in the fact that even in well known preparative works[37] the statement is found that aldehydes can be converted by diazomethane into the corresponding methyl ketones.

Our present knowledge of the reaction between aldehydes and diazomethane is based on the investigations of Arndt, Eistert, Meerwein, Mosettig, and others.[38] The reaction depends not on a methylation of the C—H group but rather on the entering of the diazomethane into the carbonyl group of the aldehyde. First an addition product which can be designated as a diazonium betaine (VIII) is formed. (The lone electron pair of the carbon atom of the extreme formula V of diazomethane enters into the octet space of the carbon atom of the carbonyl group.) Addition product VIII, for which the formula of a dihydrofurodiazole sometimes is used, is in many cases fairly stable. In all cases, by slight warming if necessary, elementary nitrogen finally splits off. The remainder of the molecule then can stabilize itself in three ways: (*1*) by the formation of the corresponding ethylene oxide; (*2*) by the formation of the corresponding methyl ketone through anionic migration of the aldehyde hydrogen atom; or finally (*3*) by the formation of the homologue of the starting aldehyde through anionic migration of the R group. The three reactions always run side by side, the one which predominates being dependent on the nature of the R group. The homologous aldehyde can immediately react further



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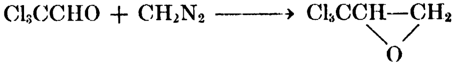
[37] *E.g.*, Weygand, *Organisch-chemische Experimentierkunst*, Voss, Leipzig, 1938, p. 505; Meyer, *Synthese der Kohlenstoffverbindungen*, Springer, Vienna, 1938, Vol. I, p. 119.

[38] Arndt and Eistert, *Ber.*, **68**, 196 (1935).

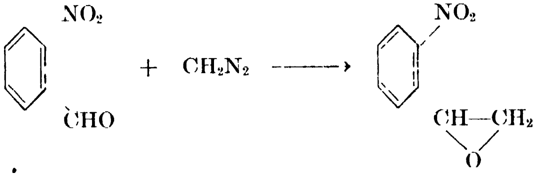
according to the same scheme so that also higher ethylene oxides and ketones are formed. The formation of the methyl ketone does not depend on a rearrangement of the first formed ethylene oxide. Such a rearrangement, which according to Tiffeneau[39] is fundamentally possible at higher temperatures, does not take place[40] under the conditions of the diazomethane reaction.

If R is a negative group,[4] the corresponding ethylene oxide is formed almost exclusively. Thus the product resulting from the reaction of diazomethane and chloral, claimed by Schlotterbeck to be 1,1,1-trichloroacetone, is in reality 1,1,1-trichloro-2,3-propylene oxide[41]:



$$Cl_3CCHO + CH_2N_2 \longrightarrow Cl_3CCH\text{—}CH_2 \text{ (}\backslash O /\text{)}$$

From *o*-nitrobenzaldehyde and diazomethane the interesting *o*-nitrophenylethylene oxide is obtained[42]:



If R is a positive group, the formation of the ethylene oxide is suppressed and in place of it is obtained the corresponding methyl ketone or the homologous aldehyde. As mentioned previously, the latter reacts further with diazomethane.

Whether the methyl ketone (under anionic migration of the hydrogen atom) or the homologous aldehyde (under anionic migration of R) and its further reaction products are formed depends on catalytic influences. It has been shown that compounds containing OH groups, such as methanol, favor the migration of R. Thus piperonal and alcohol-free diazomethane yield acetopiperone (Eq. 1, p. 524). In the presence of methanol, however, safrole oxide is formed as the product of further reaction of diazomethane on the first formed piperonylacetaldehyde (Eq. 2).[43] Benzaldehyde and *m*-nitrobenzaldehyde react in a similar manner with diazomethane. The latter, in contrast to its ortho isomer, does not give an ethylene oxide. With the exclusion of methanol it yields *m*-nitroacetophenone almost quantitatively. With the addition of methanol the reaction products of *m*-nitrophenylacetaldehyde are obtained.[40]

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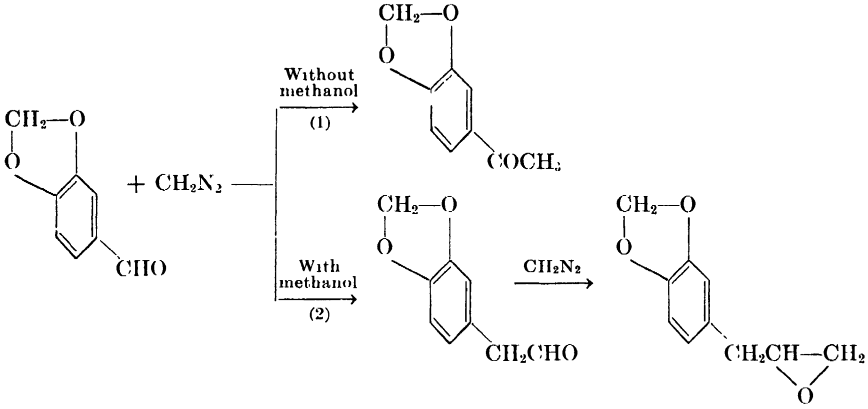
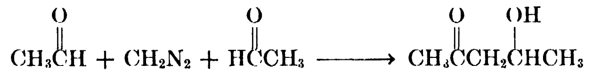
[39] Tiffeneau, *Ann. chim. phys.*, **10**, 322 (1907); *Compt. rend.*, **145**, 811 (1907).
[40] Arndt, Amende, and Ender, *Monatsh.*, **59**, 204 (1932).
[41] Arndt and Eistert, *Ber.*, **61**, 1118 (1928).
[42] Arndt, Eistert, and Partale, *Ber.*, **61**, 1107 (1928).
[43] Mosettig, *Ber.*, **61**, 1391 (1928); **62**, 1271 (1929).



The preparation of a methyl ketone in good yield, therefore, from an aldehyde which contains a positive R group, must be carried out in the absence of hydroxyl compounds. In such cases the diazomethane is not prepared from nitrosomethylurethan but from nitrosomethylurea. If, on the other hand, a large amount of methanol is added, two methylene groups are taken up with the formation of the homologous ethylene oxide as the principal product.

Many aldehydes do not react at all, or only very slowly, with diazomethane in the absence of methanol. With those aldehydes yielding essentially ethylene oxides, the addition of methanol does no harm, since the formation of ethylene oxides depends not on catalytic but only on constitutional factors. With other aldehydes, which yield either methyl ketones or the further reaction products of the first formed homologous aldehydes, the speed of reaction of the aldehydes can be increased by the addition of methanol only for the second reaction.

In the action of diazomethane on formaldehyde a mixture of products is formed, 28% of which is acetone.[44] Acetaldehyde yields with diazomethane chiefly acetone and its further reaction products. No propylene oxide is formed, but 4-hydroxy-2-pentanone is found among the byproducts, resulting from the action of 2 molecules of acetaldehyde on 1 molecule of diazomethane[45]:



$$CH_3\overset{O}{\overset{\|}{C}}H + CH_2N_2 + H\overset{O}{\overset{\|}{C}}CH_3 \longrightarrow CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{OH}{\overset{|}{C}}HCH_3$$

Schlotterbeck[34] found a similar by-product in the reaction of chloral with diazomethane.

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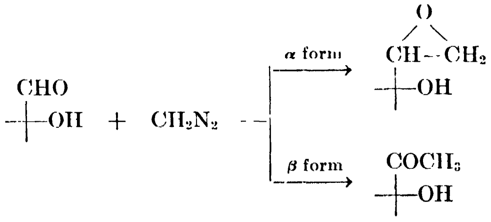
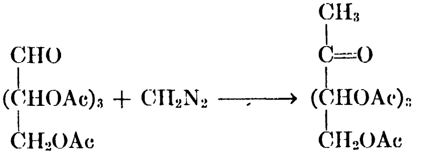
[44] Caronna, *Gazz. chim. ital.*, **66**, 772 (1936).
[45] *Cf.* Pöhls, Dissertation, Marburg, 1931.

o-Nitropiperonal, like *o*-nitrobenzaldehyde, reacts with diazomethane to give the corresponding ethylene oxide. With diazoethane, however, *o*-nitropiperonyl ethyl ketone is formed.[46] It remains to be investigated whether higher homologues of diazomethane will react with aldehydes containing a negative R group to give ketones instead of the ethylene oxides.

The influence of steric factors on the course of the reaction was observed for the first time in the reaction of aldehydes of the steroid series with diazomethane.[47] Whereas the 17-(β)-hydroxyaldehydes react with diazomethane in ether preferentially to form methyl ketones, the 17-(α)-hydroxyaldehydes give mainly ethylene oxides:



In the sugar series the conversion of aldoses into ketoses is possible. For example, the action of diazomethane on aldehydo-*d*-arabinose tetraacetate yields 1-desoxy-keto-*d*-fructose tetraacetate[48]:



$$\begin{matrix}\text{CHO} \\ | \\ (\text{CHOAc})_3 \\ | \\ \text{CH}_2\text{OAc}\end{matrix} + \text{CH}_2\text{N}_2 \longrightarrow \begin{matrix}\text{CH}_3 \\ | \\ \text{C{=}O} \\ | \\ (\text{CHOAc})_3 \\ | \\ \text{CH}_2\text{OAc}\end{matrix}$$

In addition to the preparative importance associated with the reaction between aldehydes and diazomethane, considerable use of the reaction has been made in the determination of fine structural differences. As mentioned previously, the course of the reaction varies according to whether the nitro group is in the ortho or meta position in relation to the aldehyde group. Thus, the insertion of a carbon atom changes the effect of a substituent accordingly. This is not only the case when the inserted carbon atom is a member of an aromatic ring, but also when a methylene group is inserted. Whereas *o*-nitrobenzaldehyde forms the ethylene oxide almost exclusively, *o*-nitrophenylacetaldehyde produces *o*-nitrophenylacetone in good yield, in the absence of methanol:

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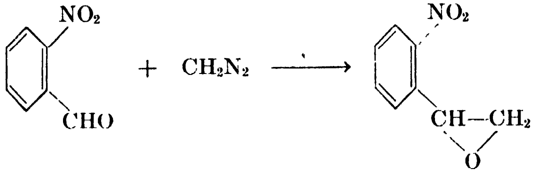
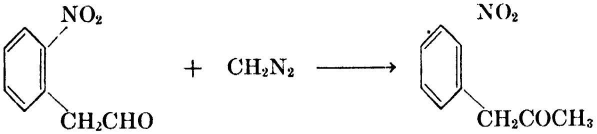
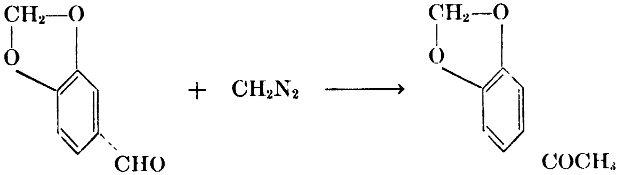
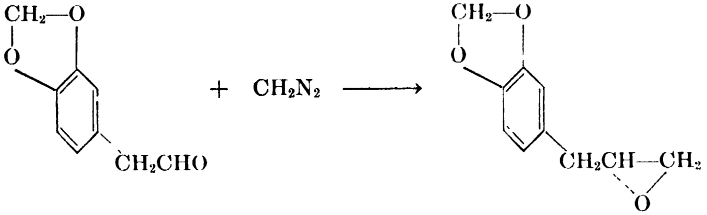
[46] Mosettig and Czadek, *Monatsh.*, **57**, 291 (1931).
[47] Prins and Reichstein, *Helv. Chim. Acta*, **24**, 945 (1941).
[48] Wolfrom, Weisblat, Zophy, and Waisbrot, *J. Am. Chem. Soc.*, **63**, 201 (1941).





Likewise, in the absence of methanol piperonal yields the corresponding acetophenone, and from piperonylacetaldehyde safrole oxide is obtained:



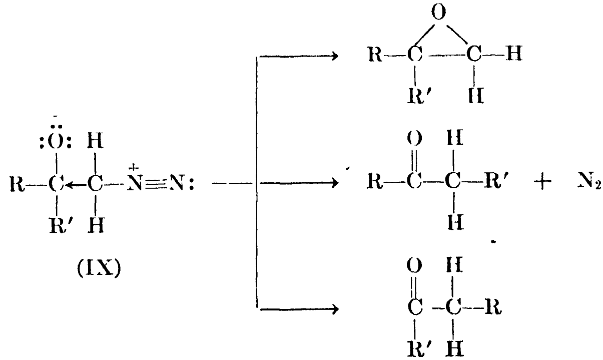


The effect of a substituent here extends alternately even across a saturated methylene group. This experimental fact plays a large role in the recent theory of the influence of substituents. It can be understood only if the general electrostatic inductive effect is accompanied by an alternating factor.[4] This substituent effect, however, disappears rapidly with distance. For example, *p*-nitrobenzaldehyde and diazomethane yield side by side about equal amounts of the corresponding ethylene oxide and the acetophenone.[40] Although the ortho and para positions generally have the same effect, this is not the case here. The systematic investigation of the reaction between aldehydes and diazomethane is likely to reveal still other important perceptions.

Some reference to the characterization of the ethylene oxides should be mentioned here. Of the best known reactions of ethylene oxides perhaps are the acid hydrolysis to form glycols and the addition of hydrogen halide to form halohydrins. With ethylene oxides which are sensitive to acids these reactions are not suitable. The halohydrin or its acyl derivative, however, can be prepared conveniently by gently warming the ethylene oxide in pyridine with gaseous hydrogen chloride or with an acid halide, respectively.[42] A further characteristic reaction is the addition of acetic anhydride in the presence of a trace of anhydrous ferric chloride.[49] Spontaneous warming results in the formation of the diacetyl derivative of the glycol. The addition of dimethylamine in the presence of water, with the formation of an amino alcohol, also can serve as proof of structure.[50]

2. Ketones

Since the reaction of aldehydes with diazomethane is not a reaction of the aldehyde hydrogen atom but rather a reaction of the carbonyl group, a similar situation should exist also in the reaction of ketones with diazomethane. Arndt and Eistert[51] have found that ketones containing negative R groups are converted, as expected, in very good yield into the corresponding ethylene oxides. Meerwein[52] has shown that ordinary ketones such as acetone also react with diazomethane in the presence of water or methanol to form both ethylene oxides and homologous ketones. For the reaction of ketones with diazomethane, therefore, a scheme can be considered which corresponds to that for aldehydes when the aldehyde hydrogen atom is replaced with an R′ group. The homologous ketones can react again with additional diazomethane and thus yield higher ketones and ethylene oxides. Which of the two possible homologous ketones is formed in the greater amount depends on the relative electron affinity of the R and R′ groups. Since ketone formation results from an anionic migration,



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[49] Knoevenagel, *Ann.*, **402**, 135 (1914).

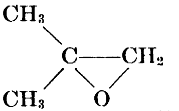
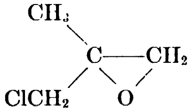
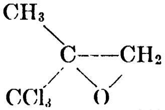
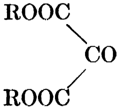
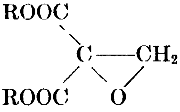
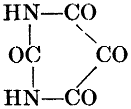
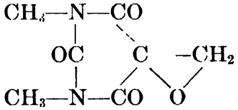
[50] *Cf.* Knorr, *Ber.*, **32**, 729 (1899). Bodforss, *Die Äthylenoxyde*, Enke, Stuttgart, 1920.

[51] Arndt and Eistert, *Ber.*, **61**, 1121 (1928). Arndt, Eistert, and Ender, *ibid.*, **62**, 44 (1929).

[52] Meerwein and Burneleit, *Ber.*, **61**, 1840 (1928). Meerwein, Bersin, and Burneleit, *ibid.*, **62**, 999 (1929). *Cf.* Bergmann, Magat, and Wagenberg, *ibid.*, **63**, 2580 (1930).

that group which has the greater electron affinity migrates preferentially. Thus, for example, a methyl group migrates more readily than does a trichloromethyl group.[40] In Table I are shown some examples of the influence of R groups on the yields of the different products.

TABLE I

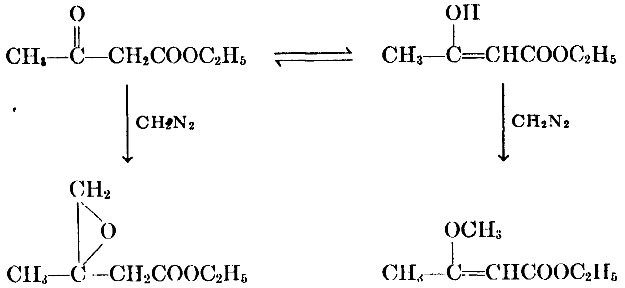
Starting material	Ethylene oxide	Ketone
CH_3COCH_3	 (about 40%)	$CH_3COCH_2CH_3$. (about 20%)
CH_3COCH_2Cl	 (about 65%)	$ClCH_2COCH_2CH_3$ (small amount)
CH_3COCCl_3	 (about 90%)	$Cl_3CCOCH_2CH_3$ (traces)
		
		

With diazomethane any non-enolizing ketone yields, besides more or less large amounts of other products, the corresponding ethylene oxide.

With ketones, which enolize readily, the enol form reacts with diazomethane with the formation of the enol methyl ether. Whether the enol methylation is the exclusive reaction or not depends on the acidity of the enol. Methyl benzoylacetate yields the enol ether exclusively, since the enol form is very strongly acidic. Acetoacetic ester on the other hand yields in addition to the enol ether (formed as the principal product[53]) small amounts of the ethylene oxide.[54] If one of the α-hydrogen atoms of acetoacetic ester is replaced by a methyl group, the acidity of the enol

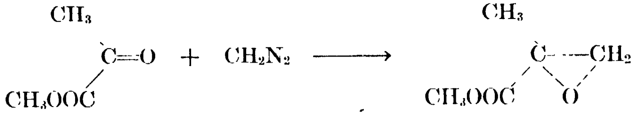
[53] von Pechmann, *Ber.*, **28**, 1626 (1895). Degner and von Pechmann, *ibid.*, **30**, 646 (1897).

[54] Arndt, Loewe, Severge, and Türegün, *Ber.*, **71**, 1640 (1938).



form is lowered to the extent that the formation of the ethylene oxide becomes the favored reaction.[55]

If a carbonyl compound yields with diazomethane the corresponding ethylene oxide exclusively, even though its hypothetical enol form ought to be sufficiently acidic to form an enol ether, then it can be concluded that no enolization takes place. In this way Arndt[56] was able to show that pyruvic acid and its ester in neutral medium exist exclusively in the keto form. They yield with diazomethane no trace of enol ether, although the enol of methyl pyruvate, anticipated theoretically and shown experimentally in the actually enolized methyl 9-fluoreneglyoxylate, ought to be sufficiently acidic to form the enol ether rapidly. From methyl pyruvate and diazomethane only the ethylene oxide is obtained, besides small amounts of aldolizing products:



Cyclic ketones also react with diazomethane according to this general scheme, with the formation of the corresponding ethylene oxides and the homologous cyclic ketones. The migration of R or R′ here results in ring enlargement.

From cyclohexanone and diazomethane Mosettig and Burger[57] obtained cycloheptanone, cyclooctanone, and the pentamethylene ethylene oxide. The reaction has been applied to other cyclic ketones by various investigators.[58] It should be noted that not all cyclic ketones undergo

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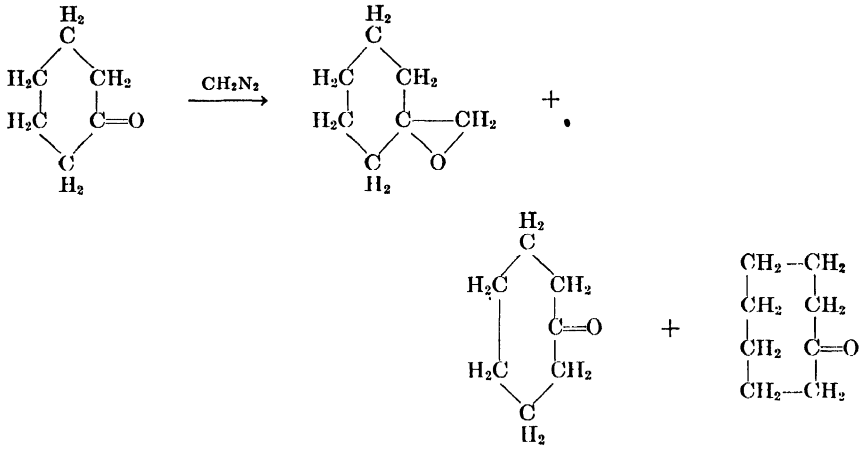
[55] Arndt, Loewe, and Beyer, *Ber.*, **74**, 1460 (1941).

[56] Arndt, Ozansoy, and Üstunyar, *Rev. faculté sci. univ. Istanbul*, **4**, No. 1–2, 83 (1939).

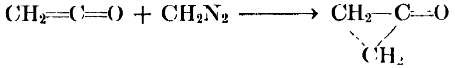
[57] Mosettig and Burger, *J. Am. Chem. Soc.*, **52**, 3456 (1930).

[58] Giraitis and Bullock, *J. Am. Chem. Soc.*, **59**, 951 (1937). Kohler, Tishler, Potter, and Thompson, *ibid.*, **61**, 1057 (1939). Meerwein, German Patent, 579,309; *Chem. Abstracts*, **27**, 4546 (1933). Robinson and Smith, *J. Chem. Soc.*, **1937**, 371. Adamson and Kenner, *ibid.*, **1939**, 181. Barbier, *Helv. Chim. Acta*, **23**, 523 (1940). Steadman, *J. Am. Chem. Soc.*, **62**, 1606 (1940). Qudrat-i-Khuda and Ghosh, *J. Indian Chem. Soc.*, **17**, 19 (1940).



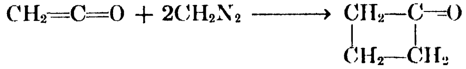
ring enlargement with equal facility. The yield of cyclic ketone, which in the conversion of cyclohexanone into cycloheptanone is 63%, falls off to 45% for cyclooctanone and to about 20% for cyclononanone and cyclodecanone. Unfortunately the reactivity of the carbonyl group passes through a minimum at the ring size most difficult to prepare by ring closure methods. Ring enlargement again becomes the favored reaction when applied to ketones having 15 or more ring members.[59] This is in complete agreement with the work of Ziegler[60] on the formation of cyclic ketones.

Ketene, which can be looked upon as the simplest cyclic ketone, also reacts with diazomethane with ring enlargement.[61] In the reaction with excess ketene, cyclopropanone is formed, which can be isolated in the form of its hydrate or, in the presence of methanol, its hemiacetal:



$$CH_2{=}C{=}O + CH_2N_2 \longrightarrow \underset{CH_2}{CH_2{-}C{=}O}$$

On standing, the hydrate isomerizes to propionic acid. From ketene and excess diazomethane, cyclobutanone is obtained:



$$CH_2{=}C{=}O + 2CH_2N_2 \longrightarrow \begin{array}{l} CH_2{-}C{=}O \\ CH_2{-}CH_2 \end{array}$$

The action of diazomethane on cyclobutanone has not yet been investigated. Cyclopentanone yields chiefly cycloheptanone. Fundamentally, the reaction with diazomethane permits the synthesis of poly-membered cyclic systems from the simplest cyclic ketone.

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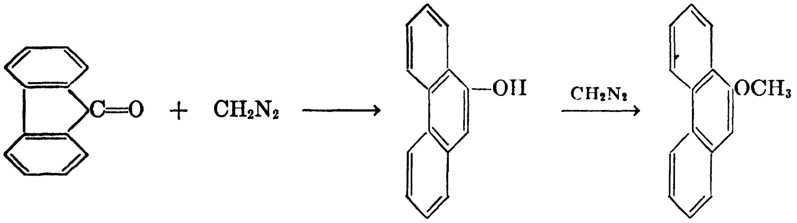
[59] Schroeder, Dissertation, Harvard, 1939. Pauli, Dissertation, Marburg, 1934. Pohls, Dissertation, Marburg, 1931.

[60] Ziegler and Aurnhammer, *Ann.*, **513**, 43 (1934). *Cf.* Ruzicka, Brugger, Pfeiffer, Schinz, and Stoll, *Helv. Chim. Acta*, **9**, 499 (1926).

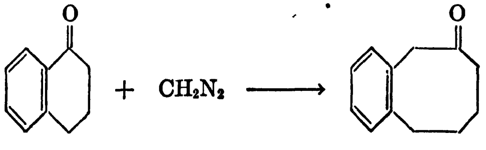
[61] Lipp and Köster, *Ber.*, **64**, 2823 (1931). Lipp, Buchkremer, and Seeles, *Ann.*, **499**, 20 (1932).

With the cyclic ketones the ratio of the ethylene oxide formed to the homologous ketone formed appears not to be essentially influenced by the addition or exclusion of methanol. The other rules apply in general as in the open ketones and may depend on steric considerations. Thus, for example, 2-chlorocyclohexanone yields 2-chlorocycloheptanone almost quantitatively and only small amounts of the ethylene oxide.[58] 2-Methylcyclohexanone, as expected, gives a mixture of the isomeric methylcycloheptanones and the corresponding ethylene oxide.[58]

The ring enlargement reaction has been applied also to aromatic cyclic ketones. For example, fluorenone reacts with diazomethane to give chiefly 9-methoxyphenanthrene[62]:



α-Tetralone has been found to react with diazomethane with the formation of an eight-membered ring. Although not definitely proved, the product is believed to be a β-ketone[63]:



Diazoethane and higher homologues of diazomethane react with cyclic ketones in much the same manner as does diazomethane itself. The reactions generally are sufficiently rapid even without the addition of methanol, and the formation of ethylene oxides falls off.[58]

From 1,4-cyclohexanedione and diazomethane are obtained several products, one of which has been identified as the diethylene oxide.[64] Homologous cyclic ketones and ethylene oxides are probably among the other products.

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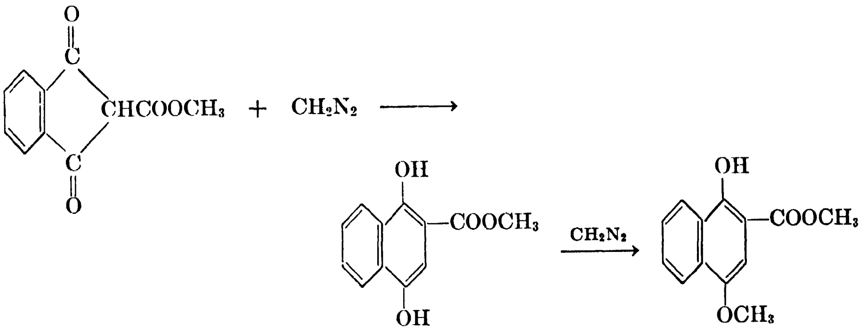
[62] Schultz, Schultz, and Cochran, *J. Am. Chem. Soc.*, **62**, 2902 (1940). *Cf.* Cook and Schoental, *J. Chem. Soc.*, **1945**, 288.

[63] Thompson, *J. Am. Chem. Soc.*, **66**, 156 (1944).

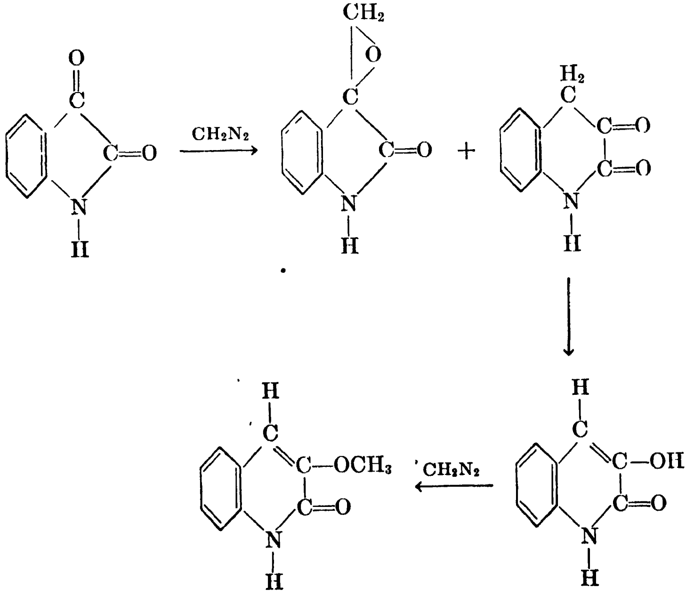
[64] Vincent, Thompson, and Smith, *J. Org. Chem.*, **3**, 603 (1939).

Methyl 1,3-indandione-2-carboxylate reacts with diazomethane to give methyl 1,4-dihydroxy-2-naphthoate or its 4-methyl ether[65]:



Whether an ethylene oxide also is formed is not known.

Isatin[66] is converted by diazomethane into 3-hydroxycarbostyril or its 3-methyl ether. The ethylene oxide also is formed in smaller amounts.[67]



N-Hydroxyisatin reacts in a similar manner to give *N*-methoxy-3-hydroxycarbostyril and its 3-methyl ether.[68]

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[65] Hantzsch and Czapp, *Ber.*, **63**, 566 (1930). Arndt, *ibid.*, **63**, 1180 (1930).

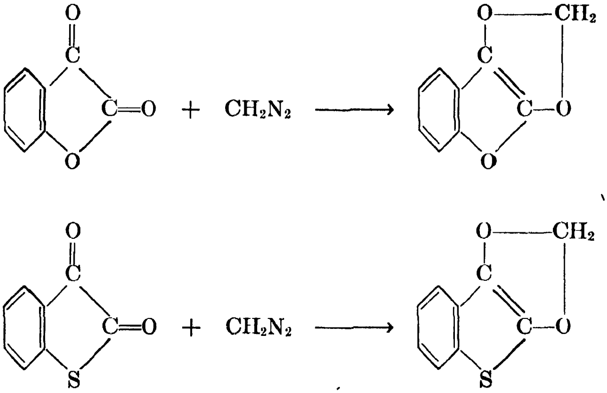
[66] Heller, *Ber.*, **52**, 742 (1919); **59**, 706 (1926).

[67] Arndt, Eistert, and Ender, *Ber.*, **62**, 48 (1929).

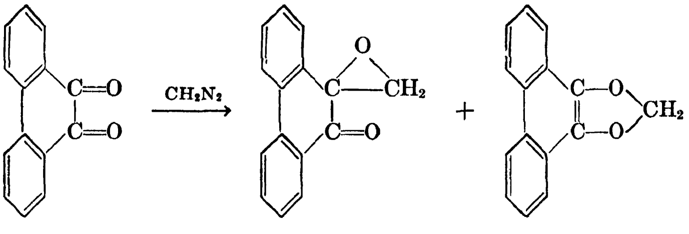
[68] Arndt, Amende, and Ender, *Monatsh.*, **59**, 210 (1932).

It should be noted that the point of attack of the diazomethane in the case of the indandione derivative is between positions 1 and 2, whereas in the case of isatin and *N*-hydroxyisatin it is between the carbonyl group in the 3 position and the benzene nucleus. The difference is due to the fact that the ring enlargement depends on the anionic migration of a group attached to the reactive carbonyl group. Since the group with the greater electron affinity always migrates, it is in the first case the $CHCOOCH_3$ group, and in the case of isatin the benzene nucleus.

The difference in behavior of analogous nitrogen, oxygen, and sulfur ring systems toward diazomethane should be mentioned. Whereas isatin undergoes ring enlargement and forms an ethylene oxide, coumarandione and thiocoumarandione yield methylene ethers:[69]



Of other *o*-quinones, only phenanthrenequinone has been investigated closely. In ether containing little methanol it forms with diazomethane a monoethylene oxide.[68] With the addition of more methanol, an oily product is obtained which, according to Biltz,[70] is the methylene ether of 9,10-phenanthrenediol:



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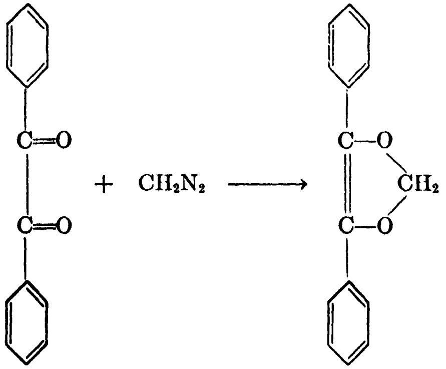
[69] *Cf.* Schönberg, Moubasher, and Mostafa, *J. Chem. Soc.*, **1941**, 348.

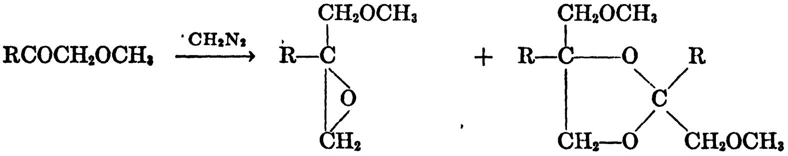
Benzil also yields such a methylene ether[70]:



Camphorquinone reacts with diazomethane, taking up two methylene groups, to form a product, the structure of which has not yet been determined.[71]

The reaction between *p*-quinone and diazomethane takes place for the most part not at the carbonyl group, but at the carbon-carbon double bond (see below). Duroquinone, however, does react with diazomethane at the carbonyl groups and yields products which are probably homologous cyclic compounds.[72]

Aliphatic α-hydroxy ketones and their ethers have been shown to react readily with diazomethane to form chiefly the corresponding ethylene oxides.[73] Cyclic acetals are also obtained, resulting from the reaction of 2 molecules of hydroxy ketone with 1 molecule of diazomethane:



α-Hydroxyacetophenone and its methyl ether first are converted slowly into the homologous 1-hydroxy-3-phenyl-2-propanone and its methyl ether, respectively, which then react readily according to the scheme of aliphatic α-hydroxy ketones and their ethers.[73]

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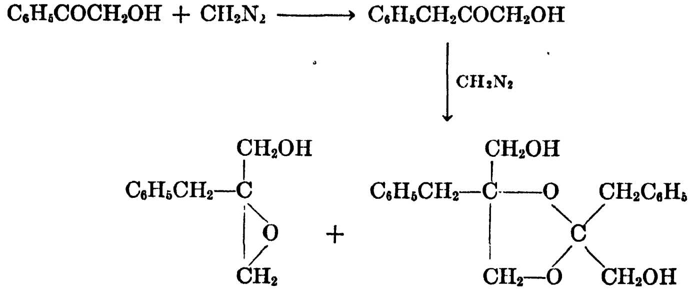
[70] Biltz and Paetzold, *Ann.*, **433**, 71, 81 (1923). *Cf.* Fieser and Hartwell, *J. Am. Chem. Soc.*, **57**, 1479 (1935).

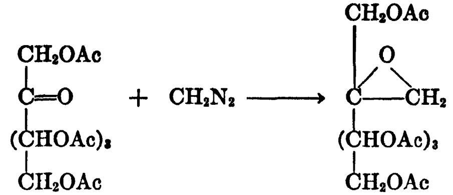
[71] Rupe and Häfliger, *Helv. Chim. Acta*, **23**, 139 (1940).

[72] Smith and Pings, *J. Org. Chem.*, **2**, 95 (1937).

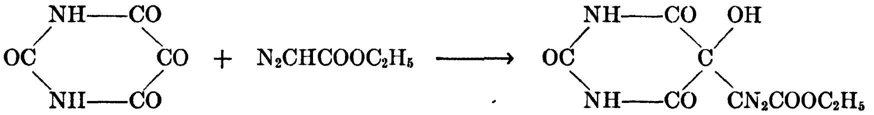
[73] *Cf.* Pauli, Dissertation, Marburg, 1934.



In the sugar series, ketoses react with diazomethane to give ethylene oxide derivatives in good yield.[74] A typical example is the reaction with keto-*d*-fructose pentaacetate:



Diazoacetic ester sometimes reacts differently with carbonyl groups than does diazomethane. Thus in the reaction of alloxan with diazoacetic ester, ethyl dialuryldiazoacetate is formed[75]:



It has been reported that many carboxylic esters, amides, and also carbon monoxide react with diazomethane in the presence of catalysts.[76] The reaction of ethyl trichloroacetate and diazomethane yields a mixture of products which have not been investigated further.[77]

3. Indirect Methylation

Ketones of the general formula RSO_2CH_2COR' yield with diazomethane the corresponding enol methyl ethers in a smooth reaction without any indication of enolization taking place.[78] This reaction also is looked upon as a reaction of the carbonyl group. However, the point of attack of the

[74] Wolfrom, Weisblat, and Waisbrot, *J. Am. Chem. Soc.*, **63**, 632 (1941).

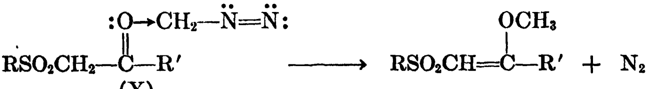
[75] Biltz and Kramer, *Ann.*, **436**, 154 (1924).

[76] Meerwein and Burneleit, *Ber.*, **61**, 1844 (1928).

[77] Meerwein, private communication. *Cf.* Meerwein and Burneleit, *Ber.*, **61**, 1844 (1928).

[78] Arndt, Amende, and Ender, *Monatsh.*, **59**, 209 (1932). Arndt and Martius, *Ann.*, **499**, 248 (1932).

diazomethane is not at the carbon atom of the carbonyl group but rather at the oxygen atom. In this case the extreme formula III (page 514) appears as the reaction formula of diazomethane. Addition product X splits off a



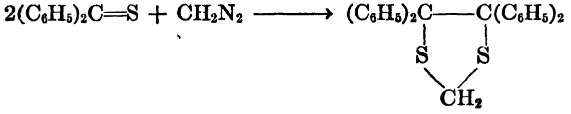
$$\underset{\text{(X)}}{RSO_2CH_2\text{—}\overset{\overset{:\ddot{O}\rightarrow CH_2\text{—}\ddot{N}=\ddot{N}:}{\|}}{C}\text{—}R'} \longrightarrow RSO_2CH{=}\overset{\overset{OCH_3}{|}}{C}\text{—}R' + N_2$$

molecule of nitrogen, and a proton of the methylene group, activated by the SO_2 group (but not strongly enough for it to form a *C*-methyl derivative), then migrates to the methylene group which comes from the diazomethane, thus forming the enol methyl ether.

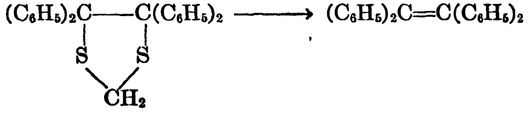
4. Thiocarbonyl Compounds

The behavior of thiocarbonyl compounds toward diazomethane shows only a slight similarity to that of carbonyl compounds. Thio aldehydes and aliphatic thio ketones, as is known, are not stable in monomeric form. The reaction of aromatic thio ketones with diazomethane has been investigated to some extent.

Most thio ketones react in such a manner that 2 molecules combine with 1 molecule of diazomethane to form the methylene ether of a 1,2-dimercaptan.[79] A typical example is the reaction of thiobenzophenone with diazomethane:



The methylene ether is converted to the tetraarylethylene by heating or by treating with phenyllithium:



Ethylene sulfides, corresponding to the ethylene oxides formed from ketones, have been obtained only by the reaction of diazomethane with Michler's thio ketone[80] and by the reaction of diphenyldiazomethane with 9-thioxanthone[81]:

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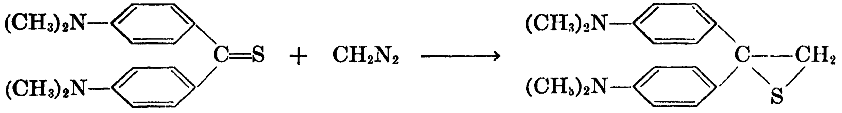
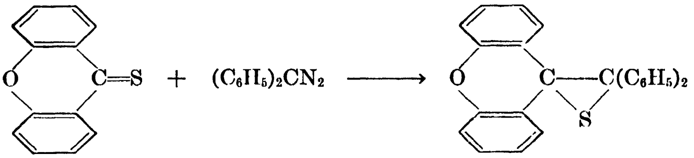
[79] Schönberg, Cernik, and Urban, *Ber.*, **64**, 2577 (1931). Schönberg, Kaltschmitt, and Schulten, *ibid.*, **66**, 245 (1933).

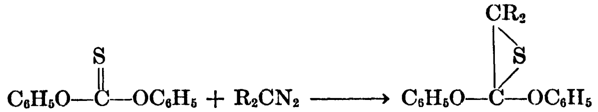
[80] Bergmann, Magat, and Wagenberg, *Ber.*, **63**, 2576 (1930).

[81] Schönberg and Nickel, *Ber.*, **64**, 2325 (1931).





Further ethylene sulfide derivatives are formed by the action of diazomethanes on derivatives of thionocarbonic acid[82]:



Whereas the CO group of ordinary carbonic and carboxylic esters does not react with diazomethane, the CS group of the thionocarbonic acid derivative, subjected to the electrostatic effect of the *O*-phenyl group, behaves somewhat as a normal keto group. The CS group of thio ketones likewise behaves as an ordinary keto group toward diazomethane when it is subjected to a large electrostatic effect,[4] as in Michler's thio ketone or in 9-thioxanthone.

VII. REACTIONS WITH ACID HALIDES

Carboxylic acid halides almost without exception react with diazomethane and its monosubstitution products. The reaction can be formulated as an acylation of diazomethane to give a diazo ketone,[83] which is obtained when the hydrogen halide splitting off is taken up by a second molecule of diazomethane with the formation of the alkyl halide and nitrogen:

$$\text{R—CO—Cl} + 2\text{CH}_2\text{N}_2 \longrightarrow \text{R—CO—CHN}_2 + \text{CH}_3\text{Cl} + \text{N}_2$$

Carboxylic acid anhydrides react, as far as has been investigated, in a corresponding manner[84]:

$$\text{R—CO—O—CO—R} + 2\text{CH}_2\text{N}_2 \longrightarrow \text{R—CO—CHN}_2 + \text{CH}_3\text{OOC—R} + \text{N}_2$$

The use of acid chlorides in the reaction has the advantage that, beside the diazo ketone, only readily volatile by-products are formed. Diazo ketones are obtained in nearly quantitative yield when the acid chloride is added slowly to a cold solution of an excess of diazomethane. If less than 2 moles of diazomethane is used per mole of acid chloride, the latter, then present in excess, reacts with the diazo ketone already formed to give a chloromethyl ketone as a by-product. The dichlorinated dioxane obtained by Nierenstein,[85] besides the chloromethyl ketones, has not been observed by other investigators.[86]

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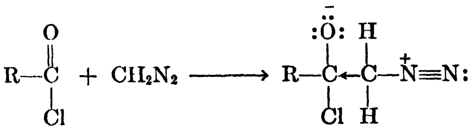
[82] Schönberg and von Vargha, *Ann.*, **483**, 176 (1930).

[83] Arndt, Eistert, and Partale, *Ber.*, **60**, 1364 (1927). *Cf.* Arndt, *Angew. Chem.*, **40**, 1099 (1927); Arndt and Amende, *Ber.*, **61**, 1122 (1928); Arndt, Eistert, and Amende, *ibid.*, **61**, 1949 (1928); Bradley and Robinson, *J. Chem. Soc.*, **1928**, 1310.

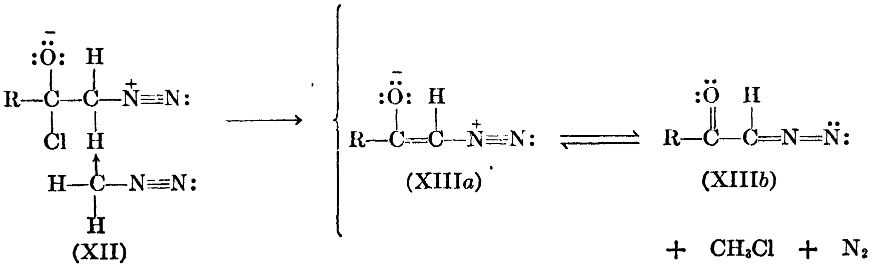
[84] Bradley and Robinson, *J. Am. Chem. Soc.*, **52**, 1558 (1930).

The reaction which leads to the formation of diazo ketones is doubtless a carbonyl reaction of the acid halide.[84,87] In the first step it corresponds to the reaction between aldehydes or ketones and diazomethane. A molecule of diazomethane enters into the carbonyl group to form a diazonium betaine (XI), sometimes interpreted as a chlorodihydrofurodiazole[88]:



(XI)

In the diazonium betaine (XI) the inductive effect of the COCl and the diazonium groups causes the hydrogen atoms of the methylene group to become so loosened that one of them forms a hydrogen bridge (XII) with a second molecule of diazomethane. Nitrogen then splits off from the second molecule of diazomethane and the remainder separates into methyl chloride and the diazo ketone:



(XII) (XIIIa) (XIIIb)

It is essential for the energy balance of the reaction that for the diazo ketones several electromeric formulas are possible, for example, the extreme formulas XIII*a* and XIII*b*, and that, therefore, resonance energy is formed in the reaction.[4]

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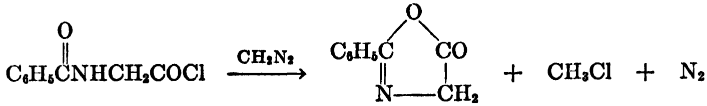
[85] Clibbens and Nierenstein, *J. Chem. Soc.*, **107**, 1491 (1915). Nierenstein, Wang, and Warr, *J. Am. Chem. Soc.*, **46**, 2551 (1924). Lewis, Nierenstein, and Rich, *ibid.*, **47**, 1728 (1925).

[86] *Cf.* Bradley and Schwarzenbach, *J. Chem. Soc.*, **1928**, 2904.

[87] Arndt and Scholz, *Ber.*, **66**, 1012 (1933).

[88] Eistert, *Ber.*, **68**, 208, 396 (1935).

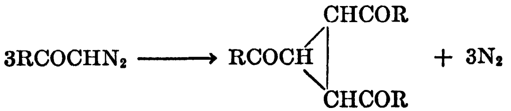
Almost all carboxylic acid chlorides that have been investigated react with diazomethane to yield diazo ketones. A few hindered acid chlorides have failed to give diazo ketones. Among these are the chloride of the acid ester of homocamphoric acid in which the acid chloride group is attached to a tertiary carbon atom[89] and mesitoyl chloride.[90] In the action of diazomethane on hippuric acid chloride no diazo ketone is formed. The diazomethane causes hydrogen chloride to split off with the formation of 2-phenyloxazolone[91]:



Sulfonic acid halides fail to react with diazomethane to form diazo ketones.[87] This fact is an important argument, therefore, that the sulfonyl group, in contrast to the carbonyl group, does not contain covalent double bonds but rather semipolar bonds between the sulfur and oxygen atoms.

Diazo ketones were obtained earlier only through complex and troublesome reactions,[92] so they had only a limited preparative value. Ever since they have become conveniently accessible from acid chlorides and diazomethane, they have been used extensively as intermediate products in syntheses.

Diazo ketones are quite stable toward alkali, but are decomposed by acids. Purely thermal decomposition of diazo ketones leads to cyclopropane derivatives; in the presence of copper compounds symmetrical diacylethylenes are formed[93]:



$$2RCOCHN_2 \longrightarrow RCOCH{=}CHCOR + 2N_2$$

Bromine and iodine react with diazo ketones in acetic acid to give dibromo- and diiodoketones, respectively[92,94]:

$$RCOCHN_2 + Br_2 \longrightarrow RCOCHBr_2 + N_2$$

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[89] Litvan and Robinson, *J. Chem. Soc.*, **1938,** 1997.

[90] *Cf.* Adams, *Organic Reactions*, Wiley, New York, 1942, Vol. I, p. 38.

[91] Karrer and Bussmann, *Helv. Chim. Acta*, 24, 645 (1941).

[92] Wolff, *Ann.*, 394, 23 (1912). *Cf.* Staudinger, Becker, and Hirzel, *Ber.*, 49, 1978 (1916).

[93] *Cf.* Grundmann, *Ann.*, 536, 29 (1938).

[94] Preobrazhenskiĭ and Kabachnik, *Ber.*, 66, 1542 (1933).

Concentrated hydrochloric and hydrobromic acids or, even better, the halogen halides in glacial acetic acid react with diazo ketones to give halomethyl ketones:[92]

$$RCOCHN_2 + HCl \longrightarrow RCOCH_2Cl + N_2$$

With these reactions it was possible to help clarify the chemistry of the halogen derivatives of acetone and acetoacetic ester.[95] Wolfrom[96] has made extensive use of these reactions in the investigation of acyclic sugar derivatives. The series of reactions leading from a carboxylic acid to a halomethyl ketone has been employed also in the synthesis of polynuclear systems, such as the cyclopentanophenanthrene series.[97]

The reducing action of hydriodic acid on diazo ketones yields methyl ketones.[96] Thus, acetophenone is obtained from α-diazoacetophenone:

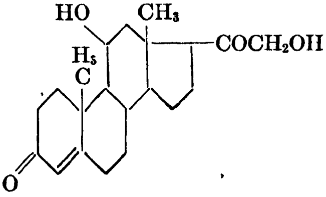
$$C_6H_5COCHN_2 \xrightarrow{HI} C_6H_5COCH_3$$

Since α-diazoacetophenone is synthesized from benzoic acid through the reaction of diazomethane with benzoyl chloride, the reduction can be formally considered, with respect to the organic acid, as a reversal of the haloform reaction.

Dilute mineral acids, such as sulfuric acid, hydrolyze diazo ketones to hydroxymethyl ketones:

$$RCOCHN_2 + H_2O \longrightarrow RCOCH_2OH + N_2$$

With the series of reactions leading from a carboxylic acid to a hydroxymethyl ketone[83] Steiger and Reichstein[98] were able to synthesize compounds of the corticosterone series:



Langenbeck[99] used the same series of reactions in the preparation of his esterase models.

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[95] Rutz, Dissertation, Breslau, 1933.

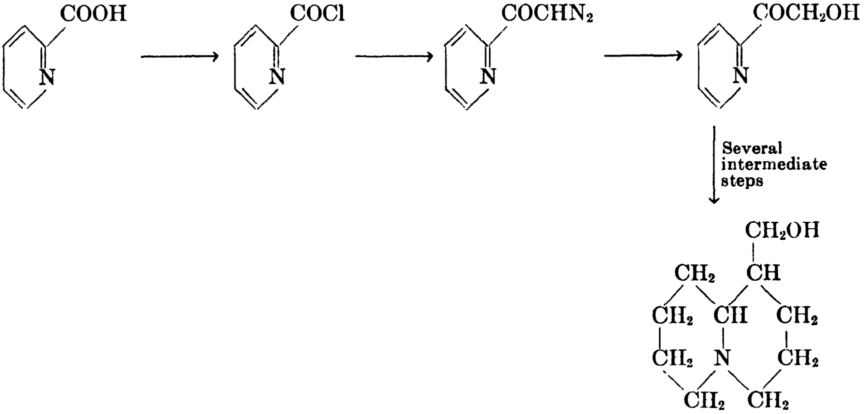
[96] Wolfrom, Weisblat, Zophy, and Waisbrot, *J. Am. Chem. Soc.*, **63**, 201 (1941). Wolfrom, Weisblat, and Waisbrot, *ibid.*, **63**, 632 (1941). Wolfrom, Waisbrot, and Brown, *ibid.*, **64**, 1701, 2329 (1942). Wolfrom, Brown, and Evans, *ibid.*, **65**, 1021 (1943). Wolfrom and Brown, *ibid.*, **65**, 1516 (1943). Wolfrom, Olin, and Evans, *ibid.*, **66**, 204 (1944). Wolfrom, Thompson, and Evans, *ibid.*, **67**, 1793 (1945).

[97] French Patent, 841,080; *Chem. Abstracts*, **34**, 1822 (1940).

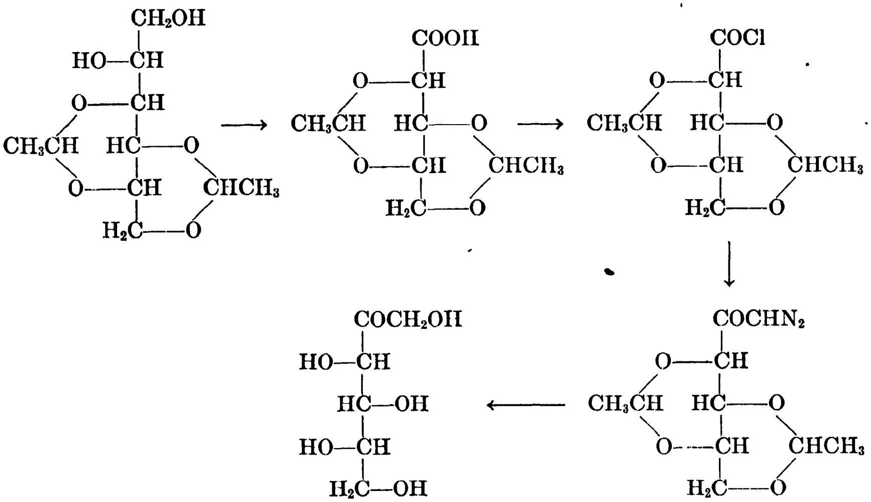
[98] Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1937).

[99] Langenbeck and Baehren, *Ber.*, **69**, 514 (1936). Lagenbeck and Hölscher, *ibid.*, **71**, 1465 (1938).

Winterfeld and von Cosel[100] made use of it in the synthesis of lupinine:



The hydroxymethyl ketone synthesis has been used by Gätzi and Reichstein[101] in the conversion of *l*-sorbitol into *l*-sorbose:



In a similar manner *d*-erythrulose has been synthesized from *d*-glyceric acid by way of its acetone derivative.[102]

Organic acids react rapidly with diazo ketones on warming to form the corresponding esters of the hydroxymethyl ketones.[103] Indifferent solvents can be used. With glacial acetic acid, for example, the acetate of the hydroxymethyl ketone is formed:

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[100] Winterfeld and von Cosel, *Arch. Pharm.*, **278**, 70 (1940).

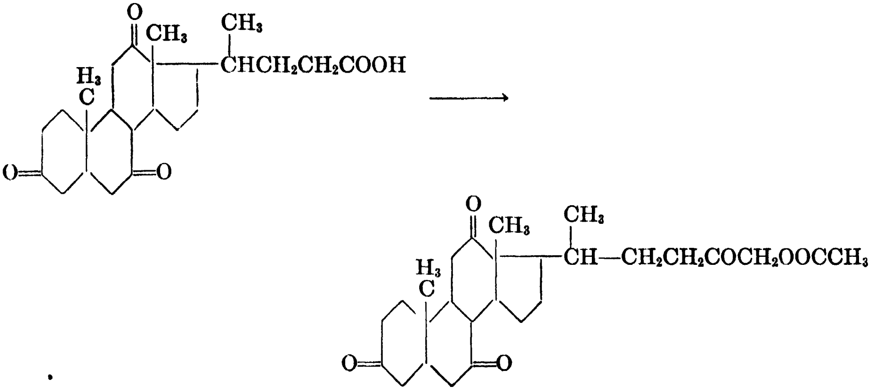
[101] Gätzi and Reichstein, *Helv. Chim. Acta*, **21**, 186 (1938).

[102] Iwadare, *Bull. Chem. Soc. Japan*, **14**, 131 (1939).

[103] Bradley and Robinson, *J. Chem. Soc.*, **1928**, 1541. Bradley and Schwarzenbach, *ibid.*, **1928**, 2904. Preobrazhenskiĭ and Kabachnik, *Ber.*, **66**, 1542 (1933).

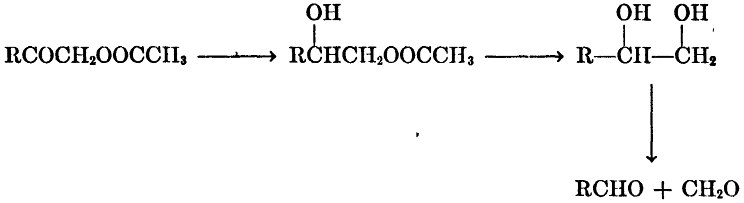
$$RCOCHN_2 + CH_3COOH \longrightarrow RCOCH_2OOCCH_3 + N_2$$

The series of reactions leading from a carboxylic acid to the ester of a hydroxymethyl ketone has been used in the synthesis of compounds of the polyhydrocyclopentanophenanthrene series.[104] Thus, from dehydrocholic acid the triketonorcholanyl acetoxymethyl ketone is obtained:



Wolfrom[96] has also applied these reactions in the synthesis of ketoses, such as *d*-sorbose and *d*-psicose.

The keto group of the ester of a hydroxymethyl ketone can be reduced to a hydroxyl group with aluminum isopropoxide,[105] thus forming the half ester of a glycol. The glycol, obtained by saponification, can be converted into an aldehyde by oxidative cleavage with lead tetraacetate[106]:



$$RCOCH_2OOCCH_3 \longrightarrow R\overset{OH}{\overset{|}{C}}HCH_2OOCCH_3 \longrightarrow R—\overset{OH}{\overset{|}{C}}H—\overset{OH}{\overset{|}{C}}H_2 \longrightarrow RCHO + CH_2O$$

This series of reactions permits, therefore, a carboxyl group under relatively mild conditions to be converted into an aldehyde group.[107]

The complete reduction of the keto group of the ester of a hydroxymethyl ketone by the Clemmensen method[108] to a methylene group is not successful, because rearrangements take place. Therefore, it is not possible to convert a carboxyl group into a β-hydroxyethyl group in this manner.[109]

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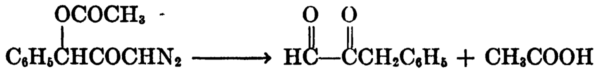
[104] French Patent, 847,129; *Chem. Abstracts*, **35**, 5653 (1941).

[105] Meerwein and Schmidt, *Ann.*, **444**, 221 (1925). Ponndorf, *Angew. Chem.*, **39**, 138 (1926). Verley, *Bull. soc. chim.*, **37**, 537, 871 (1925); **41**, 788 (1927).

[106] Criegee, Kraft, and Rank, *Ann.*, **507**, 159 (1933).

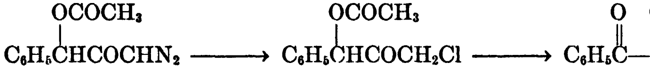
[107] Grundmann, *Ann.*, **524**, 31 (1936). *Cf.* Schöpf, Brass, Jacobi, Jorde, Mocnik, Neuroth, and Salzer, *ibid.*, **544**, 35 (1940).

The diazo ketone from *O*-acetylmandelic acid undergoes interesting transformations in the presence of acids.[110] With dilute sulfuric acid the product obtained is not the hydroxymethyl ketone. Benzylglyoxal is formed as the result of the splitting off of the acetyl group and the anionic migration of the phenyl group:



$$C_6H_5\overset{\overset{OCOCH_3}{|}}{C}HCOCHN_2 \longrightarrow H\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}CH_2C_6H_5 + CH_3COOH$$

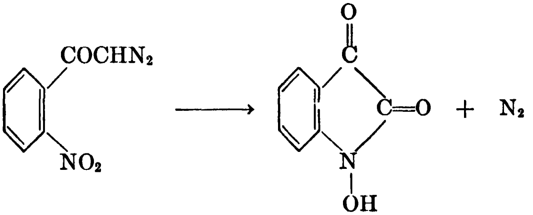
With hydrogen chloride in glacial acetic acid, the diazo ketone yields the expected chloromethyl ketone. Treatment of the latter with sodium acetate does not give an acetate derivative, but yields 1-phenyl-1,2-propanedione as the result of the anionic migration of a hydrogen atom:



$$C_6H_5\overset{\overset{OCOCH_3}{|}}{C}HCOCHN_2 \longrightarrow C_6H_5\overset{\overset{OCOCH_3}{|}}{C}HCOCH_2Cl \longrightarrow C_6H_5\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}CH_3$$

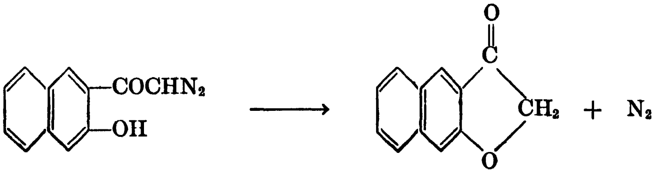
Reichstein and Schindler[111] have shown that *p*-toluenesulfonic and phosphoric esters of hydroxymethyl ketones can be prepared from diazo ketones.

Ortho-substituted aromatic diazo ketones undergo ring closure on treatment with acids when it is at all possible. Thus from α-diazo-*o*-nitroacetophenone, on warming in glacial acetic acid containing a small amount of formic acid or dilute sulfuric acid, is obtained, in very good yield, the interesting *N*-hydroxyisatin[112]:



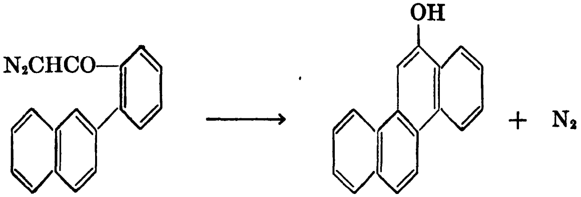
α-Diazo-3-hydroxy-2-acetonaphthone, prepared from the corresponding acid chloride and 2 molecules of diazomethane without methylation of the phenolic hydroxyl group, undergoes ring closure on treatment with acids with the formation of naphthofuran-3-one[113]:

[108] Clemmensen, *Ber.*, **46**, 1838 (1913); **47**, 51, 681 (1914).
[109] *Cf.* Dornow, *Ber.*, **73**, 156 (1940).
[110] Bradley and Eaton, *J. Chem. Soc.*, **1937**, 1913.
[111] Reichstein and Schindler, *Helv. Chim. Acta*, **23**, 669 (1940).
[112] Arndt, Eistert, and Partale, *Ber.*, **60**, 1364 (1927).
[113] Krzikalla and Eistert, *J. prakt. Chem.*, **143**, 55 (1935).



The ring closure also takes place when the hydroxyl group is protected by acetylation or methylation. Acetic acid or methanol is split off when treated with glacial acetic acid and the furanone ring is then formed.[114]

An interesting cyclization has been observed in the synthesis of polynuclear hydrocarbons. The addition of α-diazo-*o*-2-naphthylacetophenone to a 10% solution of sulfuric acid in glacial acetic acid yields 2-chrysenol[115]:



Diazo ketones are, as already mentioned, quite stable toward alkali. Use of this property can be made, for example, in the alkaline saponification of acetoxy groups that have been introduced previously. In the desoxycorticosterone synthesis, for example, the 3-acetoxy-21-diazo-5-pregnen-20-one is saponified by treatment with methanolic potassium hydroxide in the cold without affecting the diazo group.[116] The secondary hydroxyl group in the 3 position of the diazo ketone thus obtained can now be oxidized with acetone and aluminum isopropoxide to a keto group without altering the diazo group.[117] Alkaline methylations with dimethyl sulfate are also possible with diazo ketones containing hydroxyl groups by working cautiously in the cold.

At higher temperatures, on the other hand, especially in the presence of metallic catalysts (colloidal silver, platinum, or copper), a diazo ketone in alkaline medium splits off nitrogen and the remaining fragment of the molecule undergoes rearrangement whereby, with the taking up of a molecule of water, a substituted acetic acid is formed[118]:

$$RCOCHN_2 + H_2O \longrightarrow RCH_2COOH + N_2$$

---

[114] Haberland and Siegert, *Ber.*, **71**, 2620 (1938).
[115] Cook and Schoental, *J. Chem. Soc.*, **1945**, 288.
[116] Reichstein and von Euw, *Helv. Chim. Acta*, **22**, 1209 (1939); **23**, 136 (1940).
[117] Reichstein and Fuchs, *Helv. Chim. Acta*, **23**, 658 (1940).
[118] Wolff, *Ann.*, **394**, 40 (1912).

If the decomposition is carried out in the presence of an alcohol, an ester is produced.[119] An amide results when ammonia or an amine is used[118]:

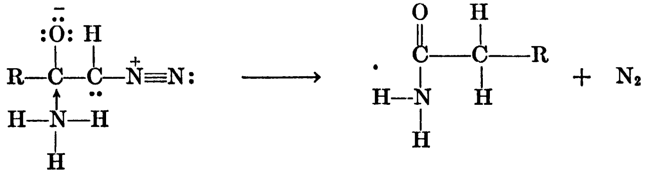
$$\begin{aligned} RCOCHN_2 &+ R'OH \longrightarrow RCH_2COOR' + N_2 \\ &+ NH_3 \longrightarrow RCH_2CONH_2 + N_2 \\ &+ R'NH_2 \longrightarrow RCH_2CONHR' + N_2 \end{aligned}$$

Since the diazo ketones are readily accessible from the corresponding carboxylic acids by way of the acid chlorides, a method for converting carboxylic acids into their higher homologues or derivatives of the homologous acids is available, which is capable of broad application. This method of synthesis proposed by Arndt and Eistert[119] is similar to the degradation of carboxylic acids according to the method of Curtius,[120] in which the acid azide appears as the intermediate product in place of the diazo ketone:

$$RCONN_2 + H_2O \longrightarrow RNHCOOH \longrightarrow RNH_2 + CO_2$$

In the Curtius degradation the rearrangement is followed by the splitting off of carbon dioxide, but in the synthesis of Arndt and Eistert this does not take place.

The rearrangement of diazo ketones into homologous acids or their derivatives can be formulated stepwise.[88] When ammonia is used, for example, the reaction begins with the entering of ammonia into the diazo ketone to form the intermediate XIV. At the diazo carbon atom is formed a lone electron pair to which a proton from the ammonia migrates. Simultaneously nitrogen splits off (under the influence of silver) and is followed by the anionic migration of the R group into the octet space of the original diazo carbon atom, with the formation of the homologous amide:



(XIV)

The rearrangement of diazo ketones into substituted acetic acids belongs to the rather frequently found class involving anionic migrations.[4] As in many such cases the rearrangement of optically active diazo ketones, in which the carbon atom attached to the carbonyl group is asymmetric, results in the formation of optically active products except in one or two instances.[121] Similar results are observed in the rearrangement of optically active acid azides. Racemization takes place in general only at high rearrangement temperatures when at the same time enolization is possible, as in the diazo ketone RR′CH—CO—CHN$_2$. The diazo ketone RR′R″-C—CO—CHN$_2$ on the other hand undergoes no racemization even in the rearrangement with boiling aniline.

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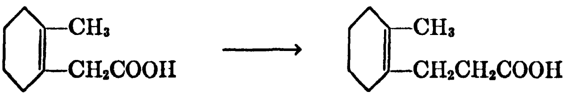
[119] Arndt and Eistert, *Ber.*, **68**, 204 (1935); **69**, 1805 (1936).
[120] Curtius, *Ber.*, **27**, 778 (1894).

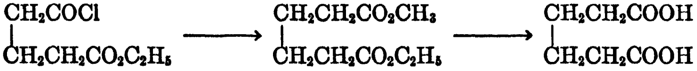
The Arndt-Eistert synthesis is fundamentally applicable to all carboxylic acids which can be converted into the corresponding acid chlorides. It also has been applied to dicarboxylic acids. In general it is recommended that, instead of producing the free homologous acids directly, the esters or amides be prepared and in those desired cases subsequently saponified. The esters and amides for the most part are formed more easily and in better yields than the free acids.

To give some idea of the scope of the Arndt-Eistert synthesis, some interesting applications of it follow. Only the initial carboxylic acid and the final product of the diazomethane synthesis and in some cases the final product of a complete synthesis are indicated.

The conversion of a β,γ-unsaturated acid into its homologue has been carried out in the synthesis of β-(2-methylcyclohexenyl)propionic acid[122]:

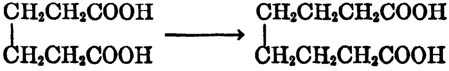


The next higher homologue of a dicarboxylic acid can be obtained through its acid ester. Thus, adipic acid has been prepared from the ester chloride of glutaric acid:[90]



$$\begin{array}{l}CH_2COCl\\ |\\ CH_2CH_2CO_2C_2H_5\end{array} \longrightarrow \begin{array}{l}CH_2CH_2CO_2CH_3\\ |\\ CH_2CH_2CO_2C_2H_5\end{array} \longrightarrow \begin{array}{l}CH_2CH_2COOH\\ |\\ CH_2CH_2COOH\end{array}$$

Dicarboxylic acids can take up two methylene groups in one operation by the Arndt-Eistert method. Thus, adipic acid has been converted into suberic acid and sebacic acid into decane-1,10-dicarboxylic acid.[123]



$$\begin{array}{l}CH_2CH_2COOH\\ |\\ CH_2CH_2COOH\end{array} \longrightarrow \begin{array}{l}CH_2CH_2CH_2COOH\\ |\\ CH_2CH_2CH_2COOH\end{array}$$

The synthesis has been applied to the preparation of heteroauxins. Thus, thionaphthene-3-acetic acid[124] and coumarone-3-acetic acid[125] have been prepared:

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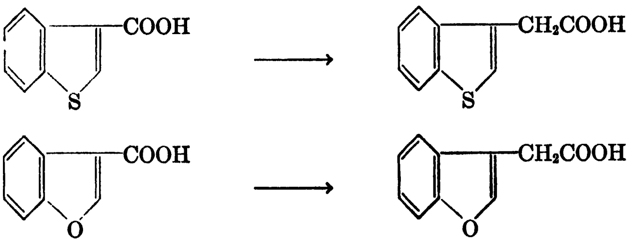
[121] Lane, Willenz, Weissberger, and Wallis, *J. Org. Chem.*, 5, 276 (1940). Lane and Wallis, *J. Am. Chem. Soc.*, 63, 1674 (1941); *J. Org. Chem.*, 6, 443 (1941).

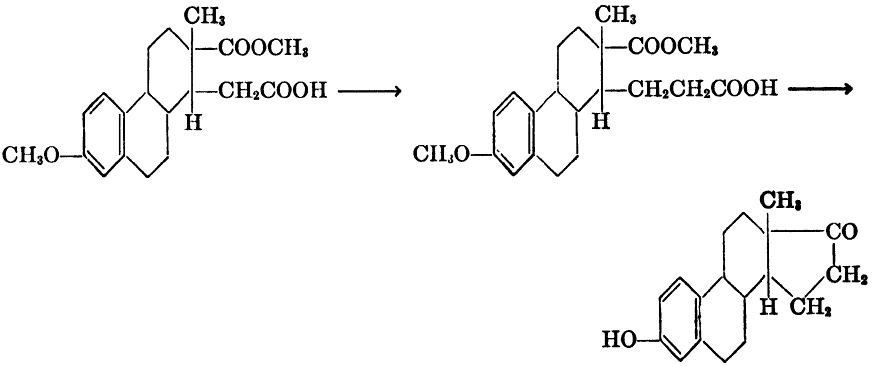
[122] Plentl and Bogert, *J. Org. Chem.*, 6, 669 (1941).

[123] Walker, *J. Chem. Soc.*, 1940, 1304.

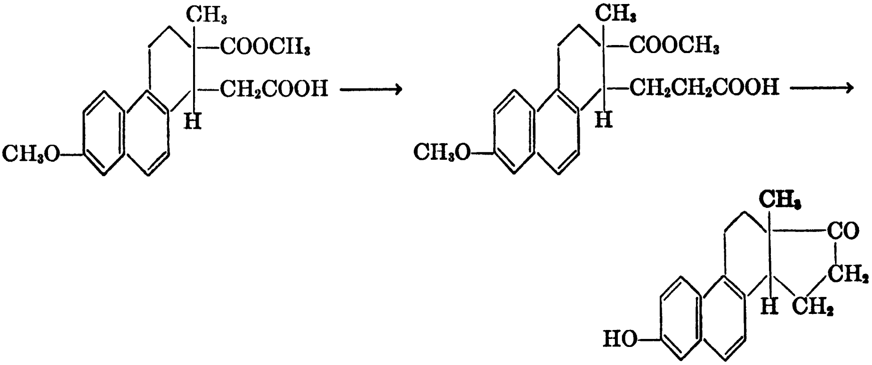
[124] Crook, Davies, and Smith, *Nature*, 139, 154 (1937). Crook and Davies, *J. Chem. Soc.*, 1937, 1697.



In the synthesis of natural substances and other related complex molecules, the Arndt-Eistert reaction has been of value because the chance of decomposition is small under the relatively mild conditions of the reaction. In the steroid series, the reaction has been applied to the synthesis of estrone[89]:



In a similar manner, the synthesis of equilenin has been carried out[126]:



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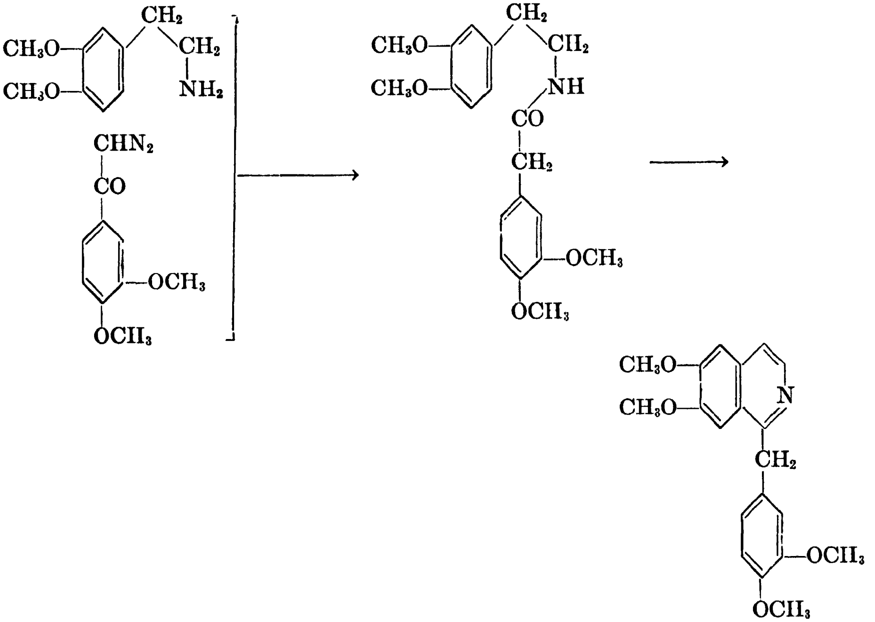
[125] Titoff, Müller, and Reichstein, *Helv. Chim. Acta*, 20, 883 (1937).

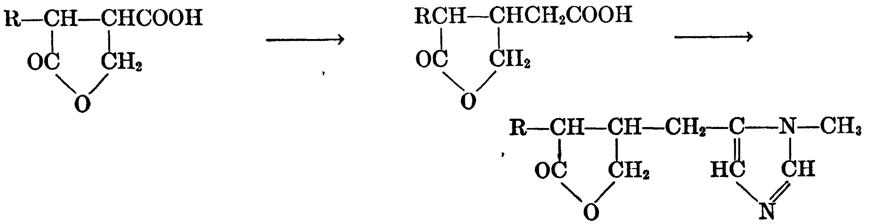
[126] Bachmann, Cole, and Wilds, *J. Am. Chem. Soc.*, 62, 827 (1940). Bachmann and Holmes, *ibid.*, 62, 2755 (1940); 63, 597 (1941). Marker and Rohrmann, *ibid.*, 62, 900 (1940).

The reaction has been extended to the opium alkaloids where papaverine has been synthesized:



The synthesis of other hydrastinine derivatives takes place in a similar manner.[127]

In the synthesis of alkaloids of *Jaborandi* leaves, the reaction has been applied to the preparation of pilocarpine[128] and pilosinine[129]:



The Arndt-Eistert reaction has been employed in the synthesis of 9-phenanthrol[130]:

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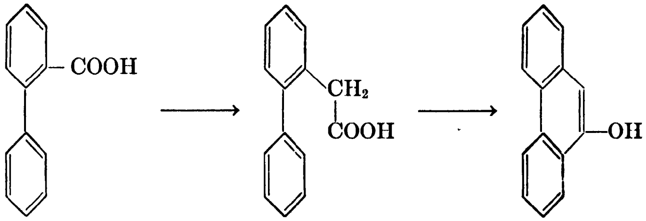
[127] *Cf*. Arndt and Eistert, German Patent, 630,953 [*Chem. Abstracts*, **31**, 116 (1937)]; German Patent, 650,706 [*Chem. Abstracts*, **32**, 595 (1938)]. Tomita and Satomi, *J. Pharm. Soc. Japan*, **58**, 165, 617 (1938). Schöpf and Winterhalder, *Ann.*, **544**, 69 (1940).

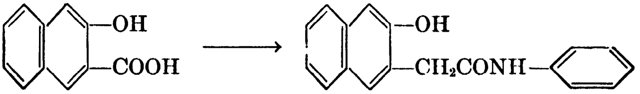
[128] Preobrazhenskiĭ, Polyakova, and Preobrazhenskiĭ, *Ber.*, **68**, 850 (1935).

[129] Polyakova, Preobrazhenskiĭ, and Preobrazhenskiĭ, *J. Gen. Chem.* (*U. S. S. R.*), **9**, 1402 (1939).

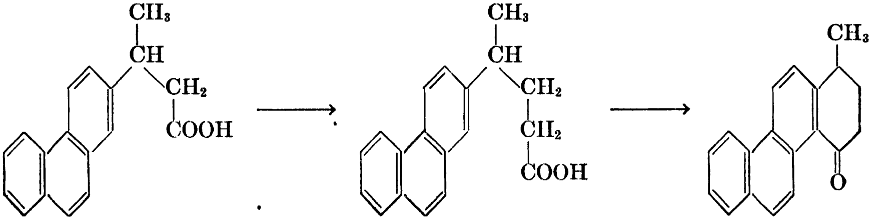
[130] Schönberg and Warren, *J. Chem. Soc.*, **1939**, 1838.



Homonaphthol AS has been synthesized smoothly by this reaction[113]:



The Arndt-Eistert method has been used in the synthesis of chrysene derivatives. Thus, 1-methyl-4-keto-1,2,3,4-tetrahydrochrysene has been obtained[131]:



Other applications of the reaction are the syntheses of γ-phenylbutyric acid,[89] hydrocamphorylacetic acid,[89] 3,4,5-trimethoxyphenylacetic acid,[132] dibenzofurylacetic acids,[133] and anthraquinonylacetic acids.[119] The reaction has also been employed in the synthesis of benzanthracene derivatives,[134] a cholanthrene derivative,[135] sugar derivatives,[96] and pyridine derivatives.[136]

Interesting derivatives of 7-pyrindole have been obtained from 2-aminopyridine-3-carboxylic acid.[137] This acid is readily converted into the corresponding diazo ketone, but the latter does not yield 2-aminopyridine-3-acetic acid according to the Arndt-Eistert reaction. Treatment of the diazo ketone with dimethylaniline causes nitrogen to split off with the cor-

[131] Bachmann and Struve, *J. Org. Chem.*, **5**, 416 (1940).

[132] Slotta and Müller, *Z. physiol. Chem.*, **238**, 16 (1936).

[133] Gilman, Parker, Bailie, and Brown, *J. Am. Chem. Soc.*, **61**, 2844 (1939). Gilman and Cheney, *ibid.*, **61**, 3155 (1939).

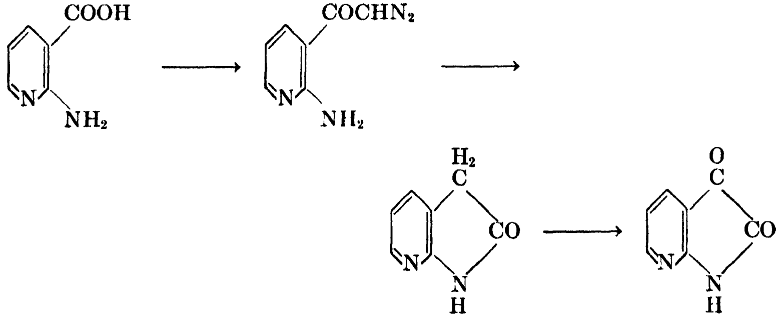
[134] Bachmann and Chemerda, *J. Org. Chem.*, **6**, 36 (1941).

[135] Fieser and Kilmer, *J. Am. Chem. Soc.*, **62**, 1354 (1940).

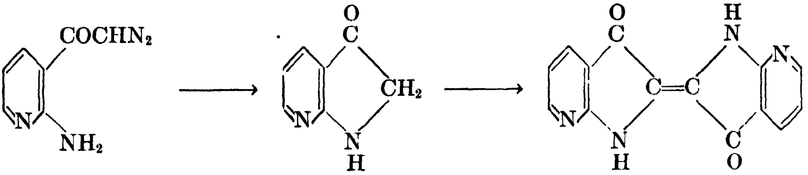
[136] Miescher and Kägi, *Helv. Chim. Acta*, **24**, 1471 (1941).

[137] *Cf.* Kägi, *Helv. Chim. Acta*, **24**, 141E (1941).

responding rearrangement to the lactam of this acid, the 7-pyroxindole. This can be oxidized by the usual methods to 7-pyrisatin:

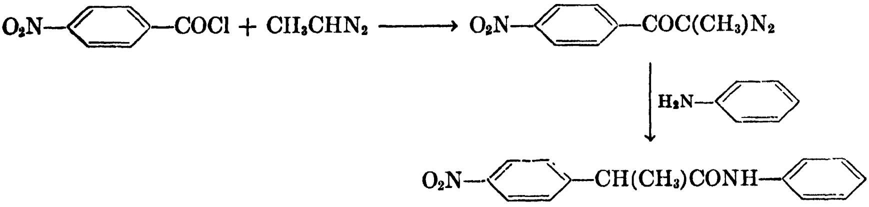


If the diazo ketone is treated with dilute sulfuric acid, the 7-pyrindoxyl is obtained along with 7,7′-bipyrindigo:



7,7′-Bipyrindigo, in contrast to the known 4,4′ isomer, is unstable in the presence of alkali and acids. It can be reduced with sodium hydrosulfite in alkali carbonate solution, however, and then absorbed on cotton with the development of a blue color.

The use of monoalkyl diazomethanes permits the synthesis of the corresponding alkyl-substituted homologous acids.[138] Thus, *p*-nitrobenzoyl chloride and diazoethane yield a diazo ketone which in the presence of aniline is converted into *p*-nitrophenylmethylacetanilide:



Other monosubstituted diazomethanes behave in a similar manner. Diazoacetic ester reacts to give a diazo keto ester[139] which can rearrange to form a substituted malonic ester[140]:

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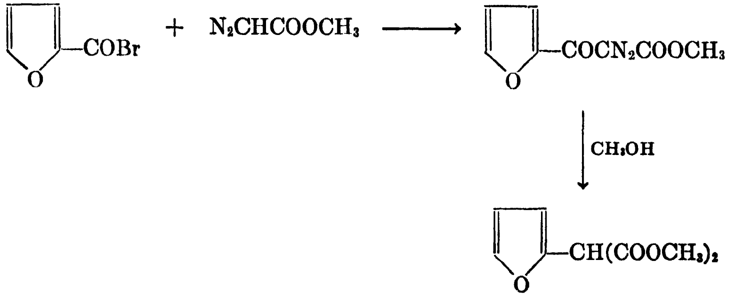
[138] Eistert, unpublished results.
[139] Schlotterbeck, *Chem.-Ztg.*, 32, 934 (1908).

$$\begin{tikzcd}
\mathrm{RCOCl} + \mathrm{N_2CHCOOC_2H_5} \arrow[r] & \mathrm{RCOCN_2COOC_2H_5} \arrow[d, "\mathrm{C_2H_5OH}"] \\
& \mathrm{RCH(COOC_2H_5)_2}
\end{tikzcd}$$

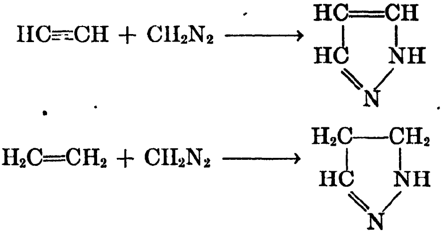
Thus, 2-furoyl bromide and methyl diazoacetate yield a diazo ketone which is converted smoothly into dimethyl 2-furylmalonate[141]:



Further examples of the Arndt-Eistert synthesis can be found elsewhere.[90]

VIII. REACTIONS WITH UNSATURATED CARBON BONDS

Diazomethane adds to acetylene and ethylene with the formation of pyrazole[142] and pyrazoline,[143] respectively:



Related to these reactions is the isomerization of vinyl diazomethane to pyrazole at ordinary temperatures[144]:

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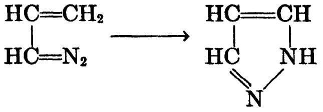
[140] Staudinger, Becker, and Hirzel, *Ber.*, 49, 1978 (1916). Staudinger and Hirzel, *ibid.*, 49, 2522 (1916). *Cf.* Schroeter, Kesseler, Liesche, and Müller, *ibid.*, 49, 2741 (1916).

[141] Reichstein and Morsman, *Helv. Chim. Acta*, 17, 1120 (1934).

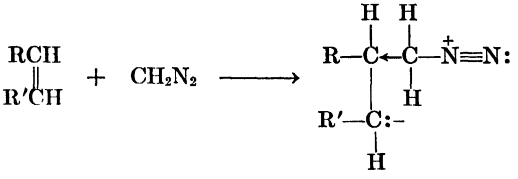
[142] von Pechmann, *Ber.*, 31, 2950 (1898). Buchner, *ibid.*, 21, 2637 (1888); 22, 842 (1889). *Cf.* Hückel, Datow, and Simmersbach, *Z. physik. Chem.*, *A*, 186, 159 (1940).

[143] Azzarello, *Atti accad. Lincei*, 14 II, 285 (1905).

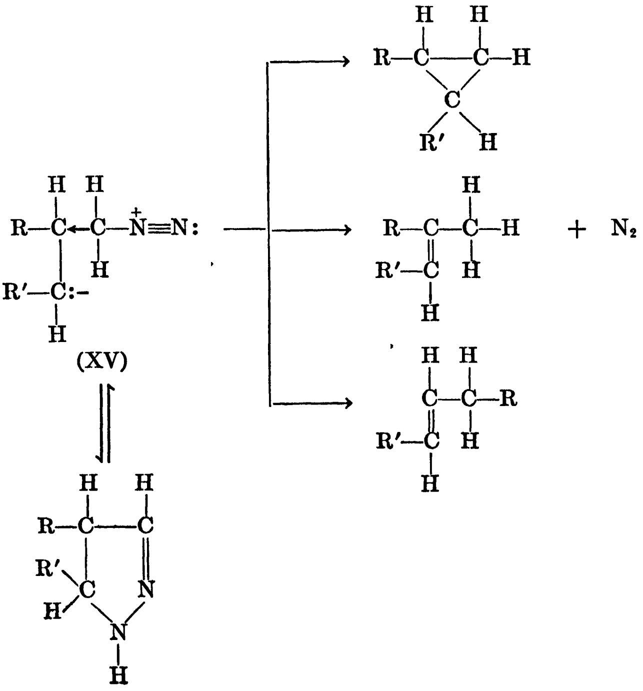
[144] Adamson and Kenner, *J. Chem. Soc.*, 1935, 289. Hurd and Lui, *J. Am. Chem. Soc.*, 57, 2656 (1935).



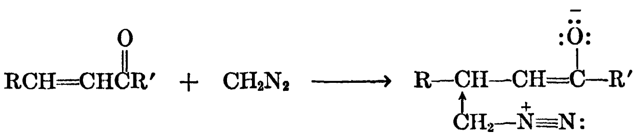
Substituted ethylenes also add diazomethane with the formation of pyrazolines. Various other products are formed, however, depending on the nature of the substitution. Although these reactions have had little systematic investigation, it appears that the reactions of the carbon-carbon double bond are similar to those of the carbonyl group. The addition probably begins here with the entering of the lone electron pair of the carbon atom of the extreme formula V (page 514) of diazomethane into the double bond, whereby a diazonium betaine (XV) is formed. This intermediate product can stabilize itself by the migration of a proton from the methylene group of the diazomethane with the formation of a pyrazoline



(XV)

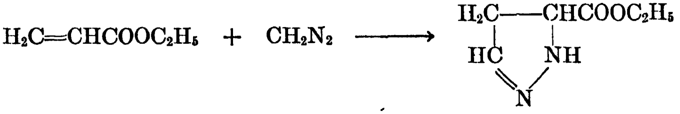


ring. It also can split off nitrogen, however, and the remaining fragment can then form a three-membered ring, a methyl-substituted product by anionic migration of a hydrogen atom, or the homologous compound by anionic migration of the R group. All of these possibilities have been observed experimentally. Evidence for the existence of the intermediate addition product before pyrazoline formation takes place has been established by von Pechmann.[145] These primary addition products are especially stable when the R′ group possesses a double bond, such as is found in a carbonyl group. 1,4 Addition of the diazomethane takes place with the formation of the diazonium enol betaine XVI, the decomposition of which then proceeds by way of the diazonium betaine XV:

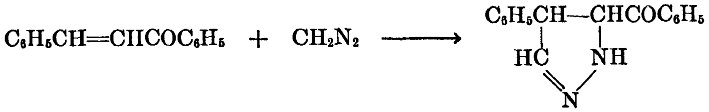


(XVI)

It has been shown by von Auwers[146] that the addition of diazomethane to α,β-unsaturated esters and ketones always proceeds in such a way that the methylene group becomes attached to the β-carbon atom. Thus, for example, ethyl acrylate reacts with diazomethane to give the corresponding pyrazoline derivative:



Benzalacetophenone adds diazomethane in a similar manner:[147]



Diazomethane also has been added to the esters of unsaturated, conjugated, dibasic acids, such as fumaric acid, with the formation of the corresponding pyrazolinedicarboxylic esters.[142,147]

The pyrazolines generally are decomposed by heating. Nitrogen is evolved and cyclopropane derivatives are formed.[148] In many cases the

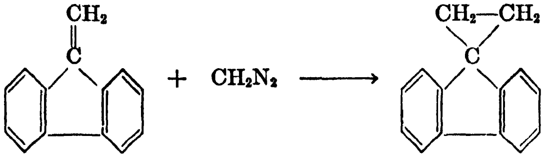
[145] von Pechmann and Seel, *Ber.*, 32, 2292 (1899).

[146] von Auwers and Cauer, *Ann.*, 470, 284 (1929). von Auwers and König, *ibid.*, 496, 27, 252 (1932). von Auwers and Ungemach, *Ber.*, 66, 1206 (1933).

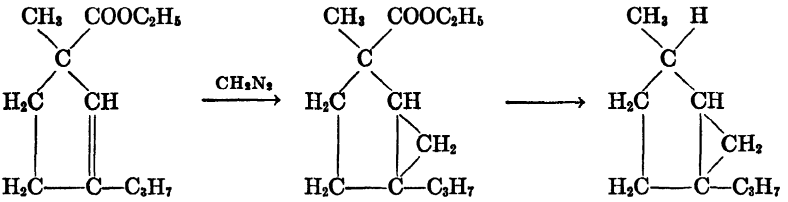
[147] Smith and Pings, *J. Org. Chem.*, 2, 23 (1937). Smith and Howard, *J. Am. Chem. Soc.*, 65, 159, 165 (1943). *Cf.* Hüttel, *Ber.*, 74, 1680 (1941).

[148] Buchner, *Ann.*, 273, 229 (1893). Gotkis and Cloke, *J. Am. Chem. Soc.*, 56, 2710 (1934).

reaction of diazomethane with an olefin does not give the corresponding pyrazoline, but immediately yields the cyclopropane derivative. The action of diazomethane on biphenylenethylene follows this course[149]:

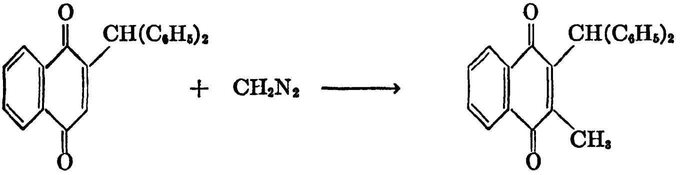


This reaction has been employed in the synthesis of thujane[150]:

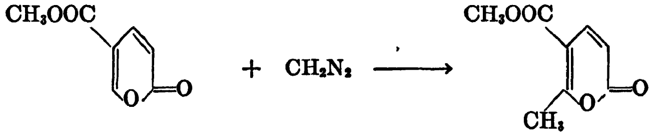


It has also been used in the pyrrole series[151] and with mesityl oxide.[152]

The reaction of an ethylene with diazomethane leading to a methyl-substituted product has been observed[153] in the case of a naphthoquinone derivative:



α-Pyrone derivatives containing a negative substituent in the 5 position undergo similar nuclear methylation in the 6 position when treated with diazomethane[154]:



If the $COOCH_3$ group in the 5 position is replaced by a hydrogen or a methyl group, the reaction does not take place. Methyl α-cyanocrotonate, when treated with diazomethane, also undergoes methylation with the formation of methyl isopropylidenecyanoacetate.[155]

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[149] Wieland and Probst, *Ann.*, **530**, 277 (1937).

[150] Guha and Krishnamurthy, *Ber.*, **70**, 2113 (1937). Rydon, *J. Chem. Soc.*, **1936**, 829.

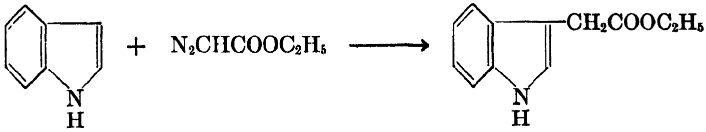
[151] Fischer and Staff, *Z. physiol. Chem.*, **234**, 105 (1935).

[152] Adamson and Kenner, *J. Chem. Soc.*, **1937**, 1551.

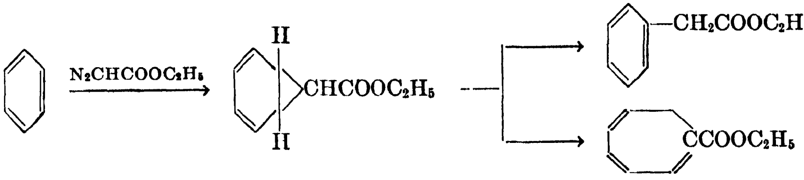
[153] Fieser and Hartwell, *J. Am. Chem. Soc.*, **57**, 1479 (1935).

[154] Fried and Elderfield, *J. Org. Chem.*, **6**, 577 (1941).

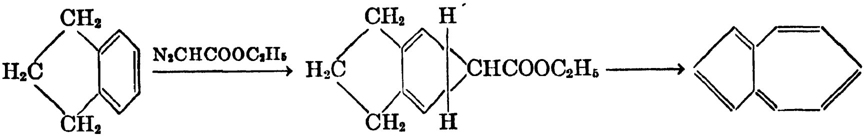
Indole reacts in a similar manner with diazoacetic ester to give ethyl 3-indoleacetate[156]:



The formation of the homologous compound resulting from the anionic migration of an R group has been observed, besides other reactions, only in the action of diazoacetic ester on aromatic compounds. Buchner[157] has shown that diazoacetic ester reacts with benzene to yield ethyl norcaradienecarboxylate, which is rearranged when heated to form ethyl phenylacetate and ethyl cycloheptatrienecarboxylate:



An interesting application is found in the synthesis of the azulene ring system. The reaction product of indan and diazoacetic ester is saponified and then heated with palladium-charcoal, whereby simultaneous decarboxylation and dehydrogenation take place[158]:



Conjugated dienes in general add diazomethane in the 1,2-manner. Thus, butadiene reacts with 1 molecule of diazomethane to give 5-vinylpyrazoline. Reaction of the latter with a second molecule of diazomethane yields 5,5′-bipyrazoline.[159]

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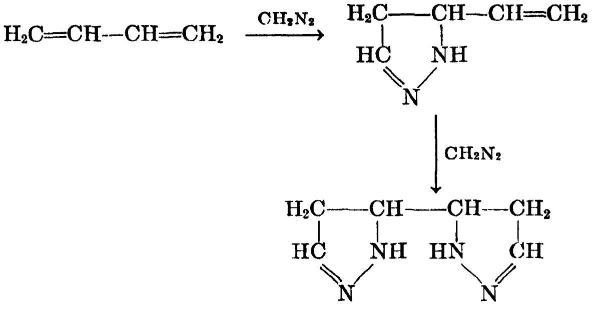
[155] Young, Andrews, Lindenbaum, and Cristol, *J. Am. Chem. Soc.*, **66**, 810 (1944).

[156] Jackson and Manske, *Can. J. Research*, **13**, 170 (1935).

[157] Braren and Buchner, *Ber.*, **33**, 684, 3453 (1900); **34**, 982 (1901). Buchner and Hediger, *ibid.*, **36**, 3502 (1903). Buchner and Scheda, *ibid.*, **37**, 931 (1904). Ruzicka and van Veen, *Ann.*, **468**, 148 (1929). Drake and Sweeney, *J. Org. Chem.*, **11**, 67 (1946).

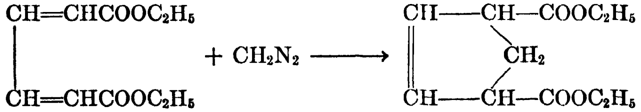
[158] St. Pfau and Plattner, *Helv. Chim. Acta*, **22**, 202 (1939). Plattner and Wyss, *ibid.*, **23** 907 (1940).

[159] Müller and Roser, *J. prakt. Chem.*, **133**, 291 (1932). *Cf.* von der Heide, *Ber.*, **37**, 2101 (1904); Staudinger, Muntwyler, Ruzicka, and Seibt, *Helv. Chim. Acta*, **7**, 390 (1924).



Diazoacetic ester adds in a similar manner. The corresponding cyclopropane derivatives are formed by heating.

If the carbon atoms in the 1 and 4 positions are adjacent to negative groups, such as $COOC_2H_5$, then 1,4 addition of diazomethane is observed. Thus, diethyl muconate reacts with diazomethane to give, after the splitting off of nitrogen, diethyl 4-cyclopentene-1,3-dicarboxylate[160]:



IX. REACTIONS WITH FREE RADICALS

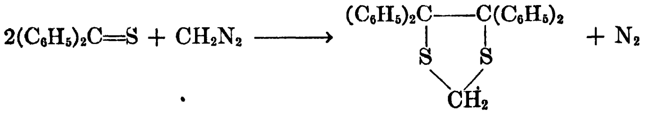
A solution of triphenylmethyl is decolorized rapidly by diazomethane with the evolution of nitrogen. Two triphenylmethyl residues combine with the methylene group of diazomethane to form hexaphenylpropane[161]:

$$2(C_6H_5)_3C\cdot + CH_2N_2 \longrightarrow (C_6H_5)_3C{-}CH_2{-}C(C_6H_5)_3 + N_2$$

Other free radicals which have been investigated behave in a similar manner. Some compounds, such as certain aromatic disulfides,[162] which can dissociate under certain circumstances, also can react in this way with diazomethane:

$$C_6H_5{-}S{-}S{-}C_6H_5 + CH_2N_2 \longrightarrow C_6H_5{-}S{-}CH_2{-}S{-}C_6H_5 + N_2$$

The formation of methylene ethers, mentioned previously, from diazomethane and thio ketones also parallels this reaction:



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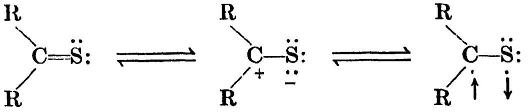
[160] Guha and Sankaran, *Ber.*, **70**, 2109 (1937). Guha and Hazra, *J. Indian Inst. Sci.*, **22A**, 263 (1939).

[161] Schlenk and Bornhardt, *Ann.*, **394**, 183 (1912).

[162] Schönberg, Rupp, and Gumlich, *Ber.*, **66**, 1932 (1933). *Cf.* Stollé, Henke-Stark, and Perrey, *ibid.*, **62**, 1112 (1929).

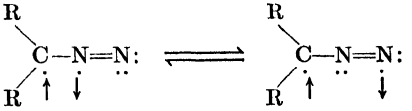
Schönberg[163] has suggested biradical formulas for the thiocarbonyl group and for the diazomethanes. Magnetic measurements of Müller[164] and Clow and Thompson,[165] however, have shown that neither the thio ketones nor the diazomethanes are paramagnetic and that free radicals, therefore, are not present here.

According to the electronic theory,[4] however, unsaturated bond systems can behave under certain circumstances like free radicals. A complete description of such a compound includes not only the usual formula and the polar extreme formula, but also formulas with uncoupled, but antiparallel, spin. Thus, the thiocarbonyl group is described by the usual formula XVII, the polar formula XVIII, and the uncoupled formula XIX.



(XVII) (XVIII) (XIX)

The diazomethanes are similarly described by uncoupled formulas XX and XXI in addition to the polar extreme formulas III, IV, and V.



(XX) (XXI)

The reactions of diazomethane in the preceding sections have been formulated by means of the polar extreme formulas, because they illustrate best the actual situations that are present. It should be kept in mind, however, that the polar mechanism, like the polar extreme formulas, is an extreme case. The other extreme is the free radical mechanism, which proceeds by way of the uncoupled formulas. Although both mechanisms are present during a reaction, the one which best describes the actual situation is used in its formulation. Thus, the polar mechanism is used in reactions involving the strongly polar carbonyl compounds. In the case of the free radicals and the disulfides it is the free radical mechanism. In the reactions of diazomethanes with carbon-carbon double bonds and thio ketones the free radical mechanism certainly takes an appreciable part. The directed addition to α,β-unsaturated carboxylic esters and ketones[146] indicates, however, that the polar mechanism here is still predominant.

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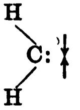
[163] Schönberg, Rupp, and Gumlich, *Ber.*, **66**, 1936 (1933). Schönberg and von Vargha, *Ann.*, **483**, 179 (1930).

[164] Müller and Muller-Rodloff, *Ber.*, **68**, 1279 (1935); *Ann.*, **517**, 147 (1935).

[165] Clow and Thompson, *Trans. Faraday Soc.*, **33**, 898 (1937).

The free methylene, which appears as the primary product from the thermal decomposition of diazomethane, should also be mentioned. It behaves like a free radical inasmuch as it readily removes mirrors of tellurium, selenium, antimony, and arsenic.[166] On the other hand zinc, cadmium, thallium, lead, and bismuth mirrors are not removed. It shows in general, however, rather the properties of a highly reactive molecule than those of a free radical.[167] This is in accord with the theory that the two free valences of the methylene are not two independent electrons, but are formulated by an electron pair and an octet deficiency with the two electrons displaying antiparallel spin (XXII).



(XXII)

An interesting reaction of diazomethane in which radical-like fragments take part is the action on zinc chloride in ether[168]:

$$(C_2H_5)_2O + ZnCl_2 + 2CH_2N_2 \longrightarrow H_5C_2—C_2H_5 + ClCH_2CH_2Cl + 2N_2 + ZnO$$

The methylene groups of 2 molecules of diazomethane form the 1,2-dichloroethane, while the ethyl groups from the ether give butane.

X. OTHER REACTIONS

1. Reduction of Diazo Groups

Diazo ketones, as mentioned previously, are reduced with hydriodic acid to the corresponding methyl ketones.[96] With hydrogen sulfide they are reduced to the hydrazones of substituted glyoxals[169]:

$$RCOCHN_2 + H_2S \longrightarrow RCOCH{=}NNH_2 + S$$

Diazoacetic ester is reduced to ethyl acetate with hydrogen in the presence of palladium in a weakly alkaline solution.[170] With zinc dust and acetic acid or aluminum amalgam in ether it is reduced to ammonia and glycine.[171]

2. Reactions with Organometallic Compounds

Diazomethane adds 2 molecules of phenylmagnesium bromide to give a product which, on hydrolysis, yields 1-phenyl-2-benzylhydrazine[172]:

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[166] *Cf.* Rice and Glasebrook, *J. Am. Chem. Soc.*, **56**, 2381 (1934).

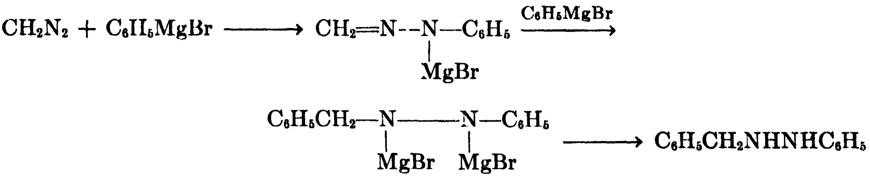
[167] Pearson, Purcell, and Saigh, *J. Chem. Soc.*, **1938**, 409.

[168] Caronna and Sansone, *Atti congr. intern. chim.*, **3**, 77 (1939).

[169] Wolff, *Ann.*, **394**, 24 (1912).

[170] Wienhaus and Ziehl, *Ber.*, **65**, 1464 (1932).

[171] Curtius, *J. prakt. Chem.*, **38**, 440 (1888). Staudinger, Gaule, and Siegwart, *Helv. Chim. Acta*, **4**, 212 (1921). Darapsky and Prabhakar, *Ber.*, **45**, 1656 (1912).



$$CH_2N_2 + C_6H_5MgBr \longrightarrow CH_2{=}N{-}\underset{MgBr}{\underset{|}{N}}{-}C_6H_5 \xrightarrow{C_6H_5MgBr}$$

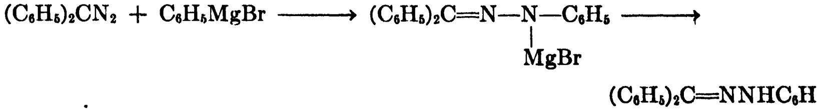
$$C_6H_5CH_2{-}\underset{MgBr}{\underset{|}{N}}{-}\underset{MgBr}{\underset{|}{N}}{-}C_6H_5 \longrightarrow C_6H_5CH_2NHNHC_6H_5$$

The reaction of diazomethane with benzylmagnesium chloride gives 1-methyl-2-benzylhydrazine; with *n*-butylmagnesium bromide it yields 1-methyl-2-*n*-butylhydrazine:[172]

$$CH_2N_2 + C_6H_5CH_2MgCl \longrightarrow CH_3NHNHCH_2C_6H_5$$

$$CH_2N_2 + C_4H_9MgBr \longrightarrow CH_3NHNHC_4H_9$$

Diphenyldiazomethane reacts with phenylmagnesium bromide to give, after hydrolysis, benzophenone phenylhydrazone:[172]



$$(C_6H_5)_2CN_2 + C_6H_5MgBr \longrightarrow (C_6H_5)_2C{=}N{-}\underset{MgBr}{\underset{|}{N}}{-}C_6H_5 \longrightarrow (C_6H_5)_2C{=}NNHC_6H_5$$

The addition of gaseous diazomethane to an ethereal solution of arsenic trichloride forms $Cl_2As{-}CH_2Cl$ and $ClAs(CH_2Cl)_2$.[173] Mercuric chloride reacts in a similar manner.[174]

3. Rearrangement Reactions

Diazomethane, without directly reacting, has sometimes brought about dehydrations. For example, under the influence of diazomethane diacetylacetone is converted into dimethylpyrone.[175] Lactone ring closure under the influence of diazomethane also has been observed.[176] Ring closures of pseudouric acid derivatives have been carried out.[177]

Through the action of diazomethane in the presence of methanol, on the other hand, lactone rings can be opened with the formation of the methyl esters of the corresponding hydroxy acids. For example, valerolactone reacts to give methyl 4-hydroxypentanoate.[178] The azlactone ring also is readily opened by this method[179]:

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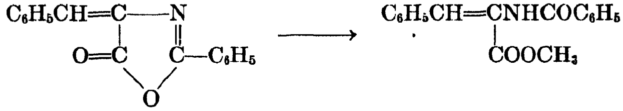
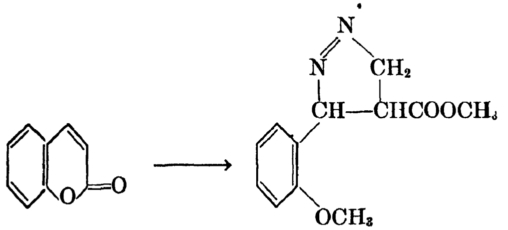
[172] Coleman, Gilman, Adams, and Pratt, *J. Org. Chem.*, **3**, 99 (1938).
[173] Braz and Yakubovich, *J. Gen. Chem.* (*U. S. S. R.*), **11**, 41 (1941).
[174] Hellerman and Newman, *J. Am. Chem. Soc.*, **54**, 2859 (1932).
[175] Collie and Reilly, *J. Chem. Soc.*, **121**, 1984 (1922).
[176] Alder and Stein, *Ann.*, **525**, 193 (1936).
[177] Biltz and Klemm, *Ann.*, **448**, 154 (1926).
[178] Spencer and Wright, *J. Am. Chem. Soc.*, **63**, 2017 (1941).



The coumarin ring is opened by the action of diazomethane with the methylation of the carboxyl and the phenolic hydroxyl groups. Simultaneously a molecule of diazomethane adds to the double bond[178]:



The action of diazomethane on saccharic acid is interesting, whereby a lactone ring is opened and simultaneously a new one is formed.[180]

It should be mentioned that the action of diazomethane on acetyl compounds in the presence of hydroxyl compounds results in the partial or complete replacement of the acetyl groups by methyl groups.[181] If hydroxyl compounds are absent, the acetyl groups remain intact.

4. Other Reactions

With compounds that gradually decompose spontaneously, diazomethane can accelerate the decomposition by methylating the cleavage products that are formed. Thus, the action of diazomethane on nitrourea yields the methylated cleavage products dimethylnitramine and methyl isocyanate.[182] *p*-Toluenesulfohydroxamic acid yields with diazomethane, besides its normal methylation product, the methylated decomposition product methyl *p*-toluenesulfinate.[183]

Diazomethane reacts with nitryl chloride to form chloronitromethane.[184] Reactions with azo[185] and nitroso[186] compounds have also been investigated.

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[179] Fischer and Hofmann, *Z. physiol. Chem.*, **245**, 139 (1937).

[180] Schmidt, Zeiser, and Dippold, *Ber.*, **70**, 2402 (1937). *Cf.* Schmidt and Kraft, *ibid.*, **74**, 33 (1941).

[181] Herzig and Tichatschek, *Ber.*, **39**, 268, 1557 (1906). Biltz, *ibid.*, **64**, 1146 (1931).

[182] Degner and von Pechmann, *Ber.*, **30**, 648 (1897).

[183] Arndt and Scholz, *Ann.*, **510**, 68 (1934).

[184] Steinkopf and Kühnel, *Ber.*, **75**, 1323 (1942).

[185] Müller, *Ber.*, **47**, 3001 (1914). Jolles, *Atti congr. intern. chim.*, **3**, 220 (1939); *Gazz. chim. ital.*, **68**, 496 (1938).

[186] von Pechmann, *Ber.*, **28**, 860 (1895). Staudinger and Miescher, *Helv. Chim. Acta*, **2**, 556 (1919).

Methylation of R—H compounds by diazomethane in the presence of sunlight has been observed.[187] For example, a mixture of 2- and 3-methyltetrahydrofurans is obtained from tetrahydrofuran.

Further reactions of aliphatic diazo compounds can be found elsewhere.[188]

Finally, isodiazomethane should be mentioned. It is produced in the form of its sodium salt when triphenylmethylsodium reacts with diazomethane.[189] Diazomethane is thus a weak acid. The anion of the sodium salt formed by the action of triphenylmethylsodium can exist in two mesomeric forms, XXIII*a* and XXIII*b*.

$$CH_2N_2 + (C_6H_5)_3CNa \longrightarrow [\underset{}{H}\text{—}\overset{..}{\underset{..}{C}}\text{—}N\equiv N: \rightleftharpoons H\text{—}\underset{..}{C}=N=\overset{..}{N}:]^-Na^+ + (C_6H_5)_3CH$$

(XXIII*a*) (XXIII*b*)

Careful acidification of the sodium salt yields both the original diazomethane and the isodiazomethane, since both extreme formulas of the sodium salt can add protons.

XI. EXPERIMENTAL PROCEDURES

1. Preparation of Nitrosomethylurea[10,190]

A solution of 100 g. of methylamine hydrochloride and 300 g. of urea in 400 cc. of water is boiled gently under reflux for 3 hours and then vigorously for 15 minutes. The solution is cooled to room temperature, 110 g. of sodium nitrite are dissolved in it, and the whole is cooled to about −10°C. and added slowly with vigorous stirring to a mixture of 600 g. of ice and 110 g. of concentrated sulfuric acid cooled in an ice-salt bath. The nitrosomethylurea immediately separates as a crystalline precipitate, which is collected on a filter, washed with cold water, and dried in a vacuum desiccator to constant weight. The yield is 110 to 122 g.

The product is best stored in a brown bottle in a refrigerator. It should not be kept above 20°C. for more than a few hours. At temperatures around 30° it may undergo sudden decomposition. In the course of several months at temperatures below 20° the product also undergoes appreciable decomposition. Purification of partially deteriorated material may be effected by recrystallization from methanol.

Other nitrosoalkylureas can be prepared in a corresponding manner.

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[187] Meerwein, Rathjen, and Werner, *Ber.*, 75, 1610 (1942).

[188] Houben, *Die Methoden der organischen Chemie*, 3rd ed., Thieme, Leipzig, 1941, Vol. IV, p. 871.

[189] Müller and Disselhoff, *Ann.*, 512, 250 (1934). Müller and Kreutzmann, *ibid.*, 512, 264 (1934).

[190] Arndt, *Organic Syntheses*, Wiley, New York, 1943, Coll. Vol. II, p. 461.

2. Preparation of Nitrosomethylurethan

Preparation of Methylurethan.[191] In a 2 liter flask provided with a mechanical stirrer, a thermometer, and two dropping funnels are placed 300 cc. of ether and 186 g. of a 33% aqueous methylamine solution. The stirred mixture is cooled to 5°C. with an ice-salt bath and 217 g. of ethyl chlorocarbonate are added dropwise at such a rate that the temperature does not rise above 5°C. When about half of the ethyl chlorocarbonate has been added, a cold solution of 80 g. of pure sodium hydroxide in 120 cc. of water is added gradually along with the rest of the ethyl chlorocarbonate with continued stirring. After the addition is completed, the reaction mixture is allowed to stand for 15 minutes. The ether layer is then separated and the aqueous solution is extracted with ether. The combined ether solutions are dried by shaking for a short time with about 10 g. of potassium carbonate in two portions. The ether is removed and the residue is distilled under reduced pressure. The yield of colorless oil boiling at 55° to 60°C. at 12 mm. is 182 to 185 g.

Nitrosation of Methylurethan.[192] In a 3 liter flask provided with a stopper which contains a thermometer, a dropping funnel extending to the bottom of the flask, and a delivery tube for evolved gases are placed 103 g. of methylurethan, 300 cc. of ether, 100 g. of ice, and 325 g. of sodium nitrite dissolved in 500 cc. of cold water. A cold solution of 300 g. of concentrated nitric acid in 300 cc. of water is then cautiously added during the course of an hour. The flask is given an occasional swirl to insure some mixing, although most of the stirring is done by the evolved gases. The mixture is allowed to stand for about 3 hours, the temperature being kept below 15°C. The ether layer first becomes red, then blue-green, and finally green. The ether layer is carefully separated (nitrosomethylurethan irritates the skin), washed twice with cold water, and then with cold potassium carbonate solution until carbon dioxide is no longer evolved. The solution is dried with potassium carbonate and the ether is removed at 45° to 50°, the last traces being removed under reduced pressure. The residue, amounting to about 100 g., can be used for the preparation of diazomethane without distillation. If so desired, the product may be distilled with caution under reduced pressure; b.p. 59° to 61°C. at 10 mm. It should be stored in a brown bottle.

3. Preparation of Nitroso-β-methylaminoisobutyl Methyl Ketone[14,193]

In a 1 liter flask provided with a stirrer, a thermometer, and a dropping funnel are placed 125 cc. of 30% aqueous methylamine solution. The solution is cooled to 5°C. and 98 g. of freshly distilled mesityl oxide are added dropwise with efficient stirring. The rate of addition is such that the temperature does not rise above 20°C. After the addition is completed, the mixture is allowed to stand without cooling for 30 minutes.

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[191] Hartman and Brethen, *Organic Syntheses*, Wiley, New York, 1943, Coll. Vol. II, p. 278.

[192] Hartman and Phillips, *ibid.*, p. 464.

The solution is then cooled to 10°C. and 100 cc. of glacial acetic acid are added dropwise at such a rate that the temperature does not rise above 15°. A solution of 83 g. of sodium nitrite in 125 cc. of water is then added dropwise to the stirred solution, the temperature of which is kept at 25° to 35°. After the addition is completed, stirring is discontinued and the mixture is allowed to stand for 6 hours or longer. The oily layer is separated from the aqueous layer and the latter is then extracted twice with ether. The combined extracts and oil are washed with dilute acetic acid and dried over calcium chloride. The ether is removed at 50°C., the last traces of low boiling material being removed under reduced pressure at 100°. The residue is sufficiently pure for the preparation of diazomethane. The yield is 110 to 128 g. If a purer product is desired, it may be distilled under reduced pressure; b.p. 119°C. at 5 mm. It should be stored in a brown bottle.

Other nitroso-β-alkylaminoisobutyl methyl ketones are prepared in a corresponding manner.

4. Preparation of Gaseous Diazomethane

FROM HYDRAZINE AND CHLOROFORM.[5] In a 500 cc. flask provided with a gas inlet tube, a dropping funnel, and a reflux condenser are placed a hot solution of 75 g. of potassium hydroxide in 180 cc. of absolute ethanol and a solution of 15 g. of hydrazine hydrate in 50 cc. of absolute ethanol. A stream of nitrogen is passed through the apparatus as a solution of 40 g. of chloroform in 50 cc. of absolute ethanol is added dropwise. A vigorous reaction takes place and the gaseous diazomethane escaping from the reflux condenser is used directly in a reaction or is collected in ice-cooled ether, dioxane, or other solvent. After the addition is completed, all of the diazomethane is displaced from the apparatus by nitrogen. The yield is 2 to 3 g.

FROM NITROSOMETHYLURETHAN.[12,194] In a flask provided with a stirrer, a dropping funnel, a gas inlet tube, and a delivery tube is placed a 6% solution of sodium in ethylene glycol. A stream of nitrogen is passed through the apparatus as nitrosomethylurethan is added dropwise. 10 cc.

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[193] Redemann, Rice, Roberts, and Ward, *Organic Syntheses*, Wiley, New York, 1945, XXV, p. 28.

[194] Burneleit, Dissertation, Königsberg, 1929.

of the glycol solution are required for every 5 cc. of the nitroso compound. The evolution of diazomethane should set in immediately. If no reaction appears, however, the addition is interrupted momentarily until the reaction begins. The escaping diazomethane is passed first through an empty, ice-cooled wash bottle and is then used directly in a reaction or collected in an ice-cooled solvent.

FROM NITROSO-β-METHYLAMINOISOBUTYL METHYL KETONE.[14] In a 150 cc. flask provided with an inlet tube, a dropping funnel, and an efficient condenser is placed a solution of 0.6 g. of sodium in 20 cc. of cyclohexanol. A stream of nitrogen is passed through the apparatus and the solution is heated at 75° to 80°C. as a mixture of 32 g. of nitroso-β-methylaminoisobutyl methyl ketone and 60 cc. of pure anisole is added dropwise. As the reaction takes place the pressure is reduced to 300 to 400 mm. The escaping vapors are passed through a condenser cooled with ice, through a U-tube filled with potassium hydroxide pellets, and finally are used directly in a reaction or collected in an ice-cooled solvent. The yield is 5.5 g.

Higher alkyl diazo compounds are prepared in a corresponding manner. The yields in general are lower.

5. Preparation of Diazomethane Solutions

FROM NITROSOMETHYLUREA WITHOUT DISTILLATION.[8,119,195] In a flask provided with a stirrer are placed 70 cc. of 45% aqueous potassium hydroxide solution and 500 cc. of ether. The mixture is cooled to 5°C. and, with vigorous stirring, 35 g. of finely powdered nitrosomethylurea are added in small portions as rapidly as the crystals dissolve. After the addition is completed, the deep yellow ethereal layer is separated from the aqueous layer by decantation or by means of a separatory funnel. The solution is dried for several hours over pellets of pure potassium hydroxide. It contains 10.5 to 12.6 g. of diazomethane.

Other solvents, such as dioxane, tetrahydrofuran (which are not miscible with strong alkaline solutions), and benzene, can be used in place of ether. Chloroform is not recommended because of its high specific gravity. In the latter case explosions have resulted from the solid nitroso compound coming in contact with the strong alkaline solution, which here forms the upper layer.

Higher alkyl diazo compounds can be prepared in a corresponding manner. The yields in general are lower.

FROM NITROSOMETHYLUREA WITH DISTILLATION.[8,195] The reaction mixture obtained above can be distilled from a water bath at 50°C. without previous separation of the alkaline layer. A stream of nitrogen may

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[195] Arndt, *Organic Syntheses*, Wiley, New York, 1943, Coll. Vol. II, p. 165.

be used to sweep the diazomethane through the apparatus. The vapors are collected in ice-cooled ether, below the surface of which is immersed the adapter attached to the condenser. The reaction mixture is distilled until the ether comes over colorless, which is usually the case when about two-thirds of it has been collected. Under no circumstances should all the ether be distilled. The solution thus obtained can be dried over pellets of pure potassium hydroxide. It contains no methanol or ammonia, but has traces of methylamine. Alkali metals should not be used for drying because of the danger of explosion.

In the preparation of higher alkyl diazo compounds, diisopropyl ether is used as solvent because of its higher boiling point.

FROM NITROSOMETHYLURETHAN.[196] In a distilling flask provided with a dropping funnel is placed a mixture of 10 cc. of nitrosomethylurethan and 50 cc. of anhydrous ether. To the gently boiling mixture 15 cc. of 25% methanolic potassium hydroxide solution are added dropwise. A stream of nitrogen may be used to sweep the diazomethane through the apparatus. The vapors are collected in ice-cooled ether, below the surface of which is immersed the adapter attached to the condenser. Distillation is continued until the contents of the flask become colorless. When frothing takes place, the distillation is interrupted immediately by cooling. The yield of diazomethane is 1.8 to 2.0 g. The solution contains methanol.

FROM NITROSO-β-METHYLAMINOISOBUTYL METHYL KETONE.[14,193] A solution of 2 g. of sodium in 66 cc. of hot cyclohexanol is cooled and the wax-like mass is cut into small pieces and added to 300 cc. of anhydrous ether in a 2-liter flask. The mixture is cooled to 10°C. and a solution of 52 g. of nitroso-β-methylaminoisobutyl methyl ketone in 600 cc. of anhydrous ether is added. The reaction mixture is distilled slowly by heating at 50°C. A stream of nitrogen may be used to sweep the diazomethane through the apparatus. The vapors are passed through a condenser held at 35°C. and are then collected in ice-cooled ether. The distillate is collected until it comes over colorless. The yield of diazomethane is 10 to 11 g.

Other alkyl diazo compounds can be prepared in a corresponding manner. The yields in general are slightly lower.

6. Reaction of Carbonyl Compounds with Nascent Diazomethane in Methanol

CONVERSION OF CYCLOHEXANONE INTO CYCLOHEPTANONE.[197] To a mixture of 500 cc. of cyclohexanone, 500 cc. of methanol, and 1 to 2 g. of finely powdered anhydrous sodium carbonate are added 10 cc. of nitrosomethylurethan, with efficient stirring. After a short time the beginning of the reaction is observed by a rise in temperature. The reaction mixture is maintained at a temperature of 20° to 25°C. by cooling in ice water as the remainder of the nitroso compound is added dropwise with continued stirring. The solution becomes pale yellow, but green or red colors indicate an unsafe concentration of explosive intermediate products. If the latter is observed, the addition is interrupted until the solution again becomes yellow. The addition of 600 g. of nitrosomethylurethan requires about 6 hours. After the addition is completed, stirring is continued for at least 30 minutes.

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[196] Houben, *Die Methoden der organischen Chemie*, 3rd ed., Thieme, Leipzig, 1930, Vol. III, p. 157.

[197] Kohler, Tishler, Potter, and Thompson, *J. Am. Chem. Soc.*, **61**, 1059 (1939).

The methanolic solution is filtered and fractionally distilled to give a 63% yield of cycloheptanone, b.p. 180° to 181°C., and a 15% yield of the ethylene oxide, b.p. 148°C.

This method can be used with carbonyl compounds, such as aldehydes, which are sensitive to alkali.

CONVERSION OF 3,3,5-TRIMETHYLCYCLOHEXANONE INTO 3,3,5- AND 3,5,5-TRIMETHYLCYCLOHEPTANONES.[198] To a mixture of 225 g. of methanol and 80 g. of 50% aqueous potassium hydroxide solution cooled at 0°C. are added 100 g. of dihydroisophorone. 74 g. of nitrosomethylurea are added in small portions with vigorous stirring at 0°. After each addition the solution is allowed to become colorless before the next portion is added. After all the nitrosomethylurea has been added, the reaction mixture is allowed to stand for several hours.

The solution is filtered from the separated potassium cyanate and neutralized with acetic acid. The methanol is removed and the residue is washed with water, dried with potassium carbonate, and fractionally distilled under reduced pressure. The ethylene oxide is collected at 64° to 68° at 11 mm., and a mixture of the two isomeric trimethylcycloheptanones at 70° to 95° at 11 mm. The isomers are separated by means of sodium bisulfite solution, with which only the 3,5,5-trimethylcycloheptanone reacts.

7. Reaction of Carbonyl Compounds with Diazomethane in the Absence of Methanol

1 mole of the aldehyde or ketone is added to a solution of 1.5 moles of diazomethane and the mixture is allowed to stand until the diazomethane has been consumed. In many cases it is necessary to warm at 30° to 50°C. to complete the splitting off of nitrogen from the intermediate diazon-

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[198] Barbier, *Helv. Chim. Acta*, 23, 523 (1940). Stoll and Scherrer, *ibid.*, 23, 943 1940).

ium betaine. This is especially true with an aldehyde containing a positive R group.

8. Preparation of Diazo Ketones[119]

1 mole of the acid chloride, undiluted or in solution, is added slowly to a solution of 2.2 to 3.0 moles of diazomethane at 0° to 10°C. with efficient stirring. Generally a brisk evolution of nitrogen takes place. The reaction with most aliphatic acid chlorides appears to be completed as soon as the addition has been made, but usually the mixture is allowed to stand at ordinary temperatures for an hour or two. With aromatic and other less reactive acid chlorides, 2 or more hours are generally allowed. Some diazo ketones crystallize from the solution as they are formed, or when the solution is cooled to about −20°C. Usually they are obtained by removing the solvent under reduced pressure at 20° to 30°. The crude diazo ketone, containing a trace of the chloromethyl ketone, generally is satisfactory for subsequent rearrangement without further purification. In many cases the diazo ketone solution as such can be immediately treated further.

In the preparation of diazo ketones from the chlorides of basic acids, such as pyridine- or quinolinecarboxylic acids, which exist in the form of their hydrochlorides, a larger excess of the diazomethane must be used to take up the additional hydrogen chloride.[109,138]

9. Preparation of Chloromethyl Ketones[92]

The conversion of a diazo ketone into a chloromethyl ketone is carried out by treating the crude diazo ketone in dioxane or glacial acetic acid with excess concentrated hydrochloric acid and then warming until the evolution of nitrogen is completed. In some cases it has been advantageous to use a solution of hydrogen chloride gas in glacial acetic acid or in ether.

10. Preparation of Methyl Ketones[96]

The conversion of a diazo ketone into a methyl ketone is carried out by treating a solution of the diazo ketone in chloroform with a 47% solution of hydriodic acid. Nitrogen is evolved and iodine is formed with the evolution of a considerable quantity of heat. When the reaction is completed, the mixture is diluted with water. The chloroform layer is separated, washed successively with water, dilute sodium thiosulfate solution, and water, and dried. The methyl ketone is obtained by removing the solvent.

11. Preparation of Hydroxymethyl Ketones[83]

The diazo ketone is dissolved in dioxane or alcohol by gentle warming. Dilute sulfuric acid is added and a vigorous evolution of nitrogen immediately sets in. Only a small amount of acid is necessary, but at least 1 mole of water must be present per mole of diazo ketone. After the evolution of nitrogen is completed, the reaction mixture is boiled for a short time.

12. Preparation of Esters of Hydroxymethyl Ketones[103]

The conversion of a diazo ketone into the acetate of a hydroxymethyl ketone is carried out by adding the crude diazo ketone in 5 g. portions to glacial acetic acid (500 to 750 cc. per mole of diazo ketone) at 50° to 60°C. The immediate evolution of nitrogen is promoted by the addition of a small boiling stone. Heat is evolved during the reaction, so cooling may be necessary. When the evolution of nitrogen has subsided, 0.1 mole of potassium acetate per mole of diazo ketone is added (for reaction with any chloromethyl ketone that may be present) and the mixture is boiled gently under a reflux condenser for about 1 hour. The reaction mixture is cooled and poured into water.

p-Toluenesulfonates of hydroxymethyl ketones are obtained by the reaction of diazo ketones with anhydrous *p*-toluenesulfonic acid in anhydrous benzene.[111]

PREPARATION OF 4-PREGNEN-21-OL-3,20-DIONE *p*-TOLUENESULFONATE. A mixture of 85 mg. of 21-diazoprogesterone and 106 mg. of high vacuum distilled *p*-toluenesulfonic acid is heated in anhydrous benzene at 50°C. for 10 minutes. The reaction mixture is cooled, diluted with ether, washed with water, and dried. The solvents are removed and the residue is recrystallized from ether-pentane. The yield is 60 mg.; m.p. 170° to 171°C.

In a similar manner sodium desoxycorticosterone phosphate is obtained from the reaction of 21-diazoprogesterone with anhydrous phosphoric acid.[111]

13. Preparation of Aldehydes[107]

CONVERSION OF STEARIC ACID INTO STEARALDEHYDE. 10 g. of stearic acid are converted to stearyl chloride with 5 g. of pure thionyl chloride. The crude acid chloride is added to a solution of excess diazomethane in ether, yielding 9.6 g. of the diazo ketone. The latter is converted with glacial acetic acid into the acetate of the hydroxymethyl ketone in 89% yield.

9.3 g. of the acetoxy ketone are dissolved in 50 cc. of absolute isopropanol and mixed with 15 cc. of a saturated solution of aluminum isopropoxide in isopropanol.[105] The reaction mixture is distilled slowly through a column at such a rate that about 50 cc. of distillate are collected during 3 hours. Fresh isopropanol is added from time to time to replace that which is distilled. As soon as no more acetone is collected in the distillate, the contents of the distilling flask are poured into excess 10% sulfuric acid solution with vigorous stirring. The precipitated 1,2-nonadecanediol is collected on a filter, washed free of aluminum with dilute acid, and recrystallized from glacial acetic acid. The yield is 6.5 g.

To a solution of 1 g. of the glycol in 30 cc. of anhydrous benzene are added several drops of glacial acetic acid. The solution is warmed at 50° to 60°C. as 1.8 g. of lead tetraacetate are added in small portions.[106] The evolution of formaldehyde takes place immediately. After the reaction mixture has been warmed at 50° for 3 hours, the excess lead tetraacetate is decomposed by adding ethylene glycol until starch iodide paper no longer turns blue. The benzene solution is washed well with water. The solvent is removed and the residue is recrystallized from ether. The yield of stearaldehyde is 0.8 g.; m.p. 63°C.

In many cases glacial acetic acid may be used instead of benzene.

14. Preparation of Homologous Acids

CONVERSION OF 1-NAPHTHOIC ACID INTO 1-NAPHTHYLACETIC ACID.[119] To a solution of diazomethane, prepared from 35 g. of nitrosomethylurea in 500 cc. of ether, is added a solution of 19 g. of 1-naphthoyl chloride in 50 cc. of anhydrous ether. After the reaction mixture has been allowed to stand at 20° to 25°C. for several hours, the ether is removed under reduced pressure, yielding 18 g. of α-diazo-1-acetonaphthone.

A solution of 15 g. of the diazo ketone in 100 cc. of dioxane is added dropwise with stirring to a mixture of 2 g. of silver oxide, 5 g. of sodium carbonate, and 3 g. of sodium thiosulfate in 200 cc. of water at 50° to 60°C. After the addition is completed, stirring is continued for 1 hour and the temperature of the mixture is raised finally to 90° to 100°. The solution is cooled, diluted with water, and acidified with dilute nitric acid. The precipitated 1-naphthylacetic acid is collected on a filter and recrystallized from water. The yield is 10 to 12 g.; m.p. 130°C.

15. Preparation of Esters of Homologous Acids

CONVERSION OF 1-NAPHTHOIC ACID INTO ETHYL 1-NAPHTHYLACETATE.[119] The diazo ketone is prepared from 1-naphthoyl chloride as described above. To a solution of 10 g. of the diazo ketone in 150 cc. of ethanol at 55° to 60°C. is added a small amount of a slurry of silver oxide, prepared from 10 cc. of 10% aqueous silver nitrate solution and stirred with 30 cc. of ethanol. The evolution of nitrogen and the formation of a silver mirror is immediately observed. When the evolution of nitrogen subsides, more of the silver oxide is introduced, and this process is repeated until all the slurry has been added. The reaction mixture is then heated under a reflux condenser for a short time, treated with charcoal, and filtered. The ethanol is removed and the residue is distilled under reduced pressure. The yield of ethyl 1-naphthylacetate is 8 to 9 g.; b.p. 175° to 178°C. at 11 mm.

The ester can be saponified to 1-naphthylacetic acid by heating under reflux with 10 *N* sodium hydroxide solution for 1 hour.

16. Preparation of Amides of Homologous Acids

CONVERSION OF 1-NAPHTHOIC ACID INTO 1-NAPHTHYLACETAMIDE.[119] The diazo ketone is prepared from 1-naphthoyl chloride as described above. To a solution of 5 g. of the diazo ketone in 100 cc. of dioxane are added 30 cc. of 20% aqueous ammonia solution. The mixture is warmed at 55° to 60°C. and 5 cc. of a 10% aqueous silver nitrate solution are added. The reaction mixture is warmed until the evolution of nitrogen is completed, and is then diluted with water. The precipitated amide is collected on a filter and recrystallized from ethanol. The yield is 4.2 g.; m.p. 181°C.

The amide can be saponified to 1-naphthylacetic acid by heating under reflux with 20% potassium hydroxide solution.

CONVERSION OF 1-NAPHTHOIC ACID INTO 1-NAPHTHYLACETANILIDE.[119] The diazo ketone is prepared from 1-naphthoyl chloride as described above. 3 g. of the diazo ketone are added in small portions to 20 g. of boiling aniline. After each addition the reaction is allowed to run to completion before the next portion is added. The mixture is boiled for a short time after all the diazo ketone has been added, cooled, and poured into dilute hydrochloric acid. The precipitated anilide is collected on a filter and recrystallized from methanol; m.p. 156°C.

Anilides can also be prepared by the method described above for 1-naphthylacetamide, the amine being used instead of ammonia.

Syntheses with Organolithium Compounds

By GEORG WITTIG

Translated and revised by JOHN R. THIRTLE

I. INTRODUCTION

Organoalkali compounds of the type RM form a series in which the reactivity under comparable conditions increases as follows:[1,2]

$$\text{RLi} < \text{RNa} < \text{RK} < \text{RRb} < \text{RCs}$$

The chemical behavior of organolithium compounds as first members of the series is intermediate between that of the other organoalkali compounds and the organomagnesium derivatives, as can be expected from the relative positions of lithium and magnesium in the periodic system.

The organolithium compounds exhibit the numerous reactions of Grignard reagents, are similarly soluble in ether, and are quite stable, in contrast to organosodium and organopotassium compounds; on the other hand, they possess a greater reactivity than organomagnesium compounds and are, for example, capable of adding to an olefinic linkage. Thus, the organolithium compounds combine the advantages of the magnesium reagents with those of the organoalkali compounds if their high sensitivity to oxygen,[3,4] requiring manipulation in an inert atmosphere, is disregarded. The majority of the reactions takes place instantaneously and almost quantitatively in the cold. The manipulations necessary in these cases are relatively simple and a few instructive examples will suffice to illustrate the methods involved.

However, aside from differences in reactivity of organolithium and organomagnesium compounds there exist differences of a more fundamental nature which will be emphasized. For example, certain compounds may fail to react with organomagnesium compounds but will react with organolithium compounds and *vice versa.* Moreover, the reaction course with

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[1] Gilman and Kirby, *J. Am. Chem. Soc.*, **55**, 1265 (1933).

[2] Gilman and Young, *J. Org. Chem.*, **1**, 315 (1936).

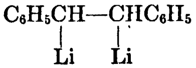
[3] Müller and Töpel, *Ber.*, **72**, 273 (1939).

[4] Gilman, Cheney, and Willis, *J. Am. Chem. Soc.*, **61**, 951 (1939).

organolithium compounds may be different from that with organomagnesium compounds in some cases.

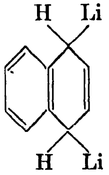
II. PREPARATION OF ORGANOLITHIUM COMPOUNDS

According to Schlenk and co-workers[5] certain unsaturated and aromatic hydrocarbons add alkali metals. For example, the following metal adducts of stilbene and naphthalene result by reaction of the hydrocarbons with lithium:



$$\underset{\text{Li}}{C_6H_5CH}—\underset{\text{Li}}{CHC_6H_5}$$

and



Since, however, this type of addition reaction gives few dilithium derivatives, it is merely mentioned here. The work of Ziegler and co-workers,[6] who showed that lithium polymerizes butadiene through metal adducts, may be mentioned in this connection (see also page 585).

For the preparation of the simple monolithium compounds, the free alkali metal can be allowed to react on the organomercury derivative in inert solvents.[7]

$$(C_2H_5)_2Hg + 2Li \longrightarrow 2C_2H_5Li + Hg$$

However, it is difficult to prepare large quantities of alkyllithium compounds by this method.

Moreover, the other old procedure of metal displacement, which was used for the preparation of phenyllithium[8] and benzyllithium[9]:

$$RMgCl + 2Li \longrightarrow RLi + LiCl + Mg \quad (R = C_6H_5 \text{ or } C_6H_5CH_2)$$

is unsatisfactory in that the lithium must react in large excess for days upon highly dilute solutions.[10]

The preparative method of choice, giving alkyl- as well as aryllithium compounds, is the replacement of the halogen atom of the alkyl and aryl halides by alkali metal. This method corresponds closely with the usual preparation of organomagnesium compounds. That this preparative possibility was examined after long delay is explained by the fact that the alkali metals generally yield hydrocarbons with alkyl or aryl halides by the Wurtz-Fittig reaction. When it was realized (Schlubach) that the Wurtz-Fittig reaction proceeds through the organometallic compound as an intermediate, the method of preparation of the latter was indicated. Ziegler and Colonius[11] established that, in the reaction of the alkyl or aryl halides with metallic lithium in particular, the lithium derivatives are formed in good yield, since they react only slowly with the organic halide still present:

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[5] See, among others, the work of Schlenk and Bergmann, *Ann.*, **463**, 72 ff. (1928).

[6] Ziegler, Jakob, Wollthan, and Wenz, *Ann.*, **511**, 64 (1934).

[7] Schlenk and Holtz, *Ber.*, **50**, 262 (1917).

[8] The formation of phenyllithium from phenylmagnesium bromide and lithium requires 8 days according to Schlenk (Schlenk, Jr., Dissertation, Berlin, 1929, pp. 19, 43).

[9] Ziegler and Dersch, *Ber.*, **64**, 448 (1931).

[10] In this connection it should be mentioned that furan and thiophene can be substituted directly in the α position by alkali metal [Gilman, Zoellner, Selby, and Boatner, *Rec. trav. chim.*, **54**, 584 (1935)].

$$RX + 2Li \longrightarrow RLi + LiX$$

Benzyllithium, however, cannot be prepared by this method, because it reacts too rapidly with benzyl chloride to form bibenzyl.

The practical knowledge which has been acquired in the preparation of organolithium compounds from the studies of Ziegler[11] and other investigators[12–25] and especially from the systematic investigations of Gilman and co-workers[26–29] may be summarized briefly as follows. The ingredient halide must be carefully purified. Bromobenzene adulterated with dibromobenzene reacts with lithium very much more sluggishly than does the pure compound. In the aliphatic series the iodides are not usable, since they react too readily with the alkyllithium, yielding the hydrocarbons. An exception is methyl iodide, from which methyllithium is formed easily in yields up to 80% in ether.[27] The optimum yields are obtained with the alkyl chlorides which react suitably in benzene or cyclohexane; in ether solution the yields decrease with increasing chain length of the halogenated hydrocarbon. Benzene or cyclohexane solutions of the aliphatic lithium compounds are stable; for example, a benzene solution of ethyllithium was still unchanged after 2 months.[30] Alkyllithium compounds, however, with the exception of methyllithium, decompose ether on long standing, with the formation of lithium alkoxides.[31–33] The aromatic halides react slowly with the metal. It is advisable, therefore, to use the halogen-metal interconversion reaction (p. 582) or to use the bromide in absolute ether. As in the Grignard reaction ether generally accelerates the preparation and reactions of organometallic compounds, while hydrocarbons such as benzene, cyclohexane, and petroleum fractions have a retarding effect.

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[11] Ziegler and Colonius, *Ann.*, 479, 135 (1930).
[12] Wittig and Leo, *Ber.*, 64, 2395 (1931).
[13] Wittig, Leo, and Wiemer, *Ber.*, 64, 2405 (1931).
[14] Wittig and Waltnitzki, *Ber.*, 67, 667 (1934).
[15] Wittig and Obermann, *Ber.*, 67, 2053 (1934).
[16] Wittig and Petri, *Ber.*, 68, 924 (1935).
[17] Wittig and Stichnoth, *Ber.*, 68, 928 (1935).
[18] Wittig and Obermann, *Ber.*, 68, 2214 (1935).
[19] Wittig and Klein, *Ber.*, 69, 2087 (1936).
[20] Wittig and Pook, *Ber.*, 70, 2485 (1937).
[21] Wittig, Pockels, and Dröge, *Ber.*, 71, 1903 (1938).
[22] Wittig and Pockels, *Ber.*, 72, 89 (1939).
[23] Wittig and Pockels, *Ber.*, 72, 884 (1939).
[24] Wittig and Petri, *Ann.*, 505, 17 (1933).
[25] Wittig and Kosack, *Ann.*, 529, 167 (1937).
[26] Gilman, Zoellner, and Selby, *J. Am. Chem. Soc.*, 54, 1957 (1932).
[27] Gilman, Zoellner, and Selby, *J. Am. Chem. Soc.*, 55, 1252 (1933).

The lithium should have the greatest possible surface. For this purpose it can be forced through a die of a sodium press, as a ribbon 1 cm. wide and 1 mm. thick, directly into absolute ether, thus keeping the metal surface bright and reactive. The lithium ribbon[34] is cut with shears into fine shreds which fall into the reaction solvent. In general, an excess of the metal is not necessary; 2 to 2.2 gram atoms of lithium per mole of organic halide suffice. A simple but cruder method of preparing the lithium is to keep it damp with toluene or xylene while pounding it to a thin wafer. Shears are used to cut thin strips nearly completely through the wafer. Cuts are then made at a right angle to the strips and the small pieces fall into the reaction solvent.

The preparation of the organolithium compound may be effected in a Schlenk tube, a Kjeldahl flask with an attached side arm containing a glass wool plug, or a three-necked flask with stirrer, dropping funnel, and reflux condenser. The apparatus should be kept in a drying cabinet until ready for use, flushed out with nitrogen, and allowed to cool in a nitrogen atmosphere. The nitrogen is taken from a cylinder and conducted through calcium chloride and phosphorus pentoxide. Generally it is unnecessary to remove traces of oxygen in the nitrogen, but the reaction mixture should be isolated from contact with air, containing oxygen, moisture, and carbon dioxide, by maintaining a slight internal pressure of nitrogen. This pressure may be obtained by an oil bubbler at an outlet from the system. The stirrer may be of the mercury seal type or may be sealed by a piece of rubber tubing slipped over the stirrer bushing. Lubrication of the rubber seal with glycerol is a standard practice.

After the addition of the lithium to the ether in the reaction flask, a quantity of the halide in ether is added. When the reaction is running smoothly, the remainder of the halide solution is added at such a rate as to cause gentle refluxing. In small preparations the lithium may be added

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[28] Gilman, Zoellner, Dickey, and Selby, *J. Am. Chem. Soc.*, **57**, 1061 (1935).

[29] Gilman, Moore, and Baine, *J. Am. Chem. Soc.*, **63**, 2479 (1941).

[30] Gilman and Kirby, *J. Am. Chem. Soc.*, **58**, 2074 (1937).

[31] Haubein, *Iowa State Coll. J. Sci.*, **18**, 48 (1943); *Chem. Abstracts*, **38**, 716 (1944)

[32] Gilman and Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).

[33] Ziegler, Crössmann, Kleiner, and Schäfer, *Ann.*, **473**, 31 (1929).

[34] Lithium wire as well as some organolithium compounds such as methyl-, ethyl-, butyl-, and phenyllithium are now available in experimental quantities from Lithaloys Corporation, 444 Madison Avenue, New York 22, New York.

directly to the ether solution of the halide, as described below. In both methods heating is continued for 0.5 to 1 hour after spontaneous refluxing subsides. When the reaction is complete, the mixture is allowed to settle and the supernatant liquid is transferred under nitrogen to a supply vessel with attached burette. Since, as mentioned before, the subsequent reactions of the organolithium compounds generally take place almost quantitatively, the content of organometallic compound is determined by allowing an aliquot portion to run into water and titrating the resulting lithium hydroxide with 0.1 *N* hydrochloric acid, methyl orange being used as indicator.

According to this general procedure the organolithium compounds are obtained in yields of 70 to 95%, based on the alkyl halide.[27,35] However, some of the titer is used to neutralize lithium hydroxide formed by contact with oxygen or moisture and, frequently, lithium ethoxide formed by cleavage of the ether. Therefore, an incorrect measure of the content of organolithium compound is obtained. Consequently a double titration method[32,33] is used for accuracy. The simpler procedure[32] consists of an initial titration as above. In a second aliquot portion the organolithium compound is coupled with benzyl chloride (see p. 584) and the lithium hydroxide and oxide and lithium ethoxide are determined by titration with acid. The difference in the titers is due to the organolithium compound and an accurate determination is obtained. The preparation of a representative of the aliphatic and of the aromatic series is illustrated below.[36]

1. *n*-Butyllithium

A. IN ETHER SOLUTION.[26–29] One-fourth to one-third of the 18.5 g. (0.2 mole) of *n*-butyl chloride in 50 cc. of absolute ether is placed in the reaction flask, 3 g. (0.43 atom) of lithium particles is added, and the flask is closed with a stopper containing a reflux condenser and a dropping funnel. The reaction begins in about 5 minutes; if necessary, warming slightly will initiate the reaction. The remaining butyl chloride in 50 cc. of ether is added dropwise. When the reaction slackens (about 45 minutes), another 50 cc. of ether is added and the reaction mixture is held at the gentle boiling point for 2 hours. After cooling and settling, the solution is transferred to the storage burette. Yield, 75 to 80%. The solution is used without undue delay, because of the tendency of ether to be cleaved by butyllithium.

B. IN BENZENE SOLUTION.[11] A solution of 9.2 g. (0.1 mole) of *n*-butyl chloride in 100 cc. of dry benzene is shaken with 2 g. (0.29 atom) of lithium particles under nitrogen in a sealed tube for 24 hours. It is ad-

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[35] Gilman, Zoellner, Selby, and Boatner, *Rec. trav. chim.*, 54, 584 (1935).

[36] The single titration method is used in the preparations cited in this chapter.

visable to add a few glass beads, since the metal otherwise becomes too thickly coated. Initial cooling is not necessary when the chloride is used. After cooling and settling, the solution of butyllithium is transferred to the storage burette. Yield, about 75%.

2. Phenyllithium[37]

A 500 cc. Kjeldahl flask is charged with 32 g. (0.204 mole) of bromobenzene which is then covered by 100 cc. of absolute ether. After the addition of 3 g. (0.43 atom) of lithium particles, the flask is attached under nitrogen to a reflux condenser and mercury trap. By slight rotation a part of the heavier bromobenzene lying on the bottom of the flask is brought into contact with the floating metal particles, whereupon the reaction starts in 2 to 5 minutes. The vigorous reaction is allowed to proceed for 20 to 30 minutes. The mixture is diluted with 50 cc. more ether and heated at boiling for 30 minutes longer. After cooling and settling, the solution is transferred under nitrogen to the storage burette. Yield, 90 to 95%.

Difficulties occur in the preparation of multinuclear aryllithium compounds, since compounds such as *p*-biphenyllithium or α-naphthyllithium[38] rapidly cleave ether and their preparation takes place too slowly in hydrocarbons. Further, the preparation of anisyllithium and related compounds leads to mixtures for reasons which are explained on page 579.

It is significant that certain lithium compounds can be obtained from such aryl halides as are attacked by magnesium only with difficulty or not at all. *p*-Bromobiphenyl and *p*-bromodimethylaniline[39] belong in this class. The latter compound gives a 95% yield of the desired lithium derivative.[27] Also in this class are aromatic chlorine compounds such as chlorobenzene, *p*-chlorotoluene, and α-chloronaphthalene. Since, conversely, dihalobenzenes such as *p*-dibromobenzene react better with magnesium than with lithium, these two metals supplement each other excellently.

The simple alkyl- and aryllithium compounds are generally colorless or nearly colorless. An exception is benzyllithium which is yellow. Unlike the other organoalkali derivatives, they dissolve in ether or benzene and a few, such as ethyllithium, dissolve in petroleum ether. For the reactions of organolithium compounds ether is the proper solvent, since it accelerates the reactions, while benzene or benzine (ligroin, etc.) retards the reactions.

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[37] Wittig, unpublished data.

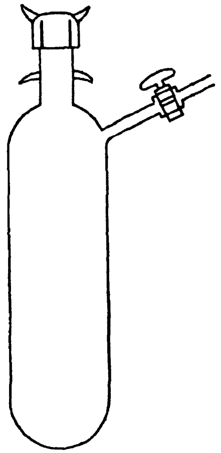
[38] Optimum conditions for this preparation are described by Müller and Töpel, *Ber.*, **72**, 273 (1939).

[39] This compound is used in color test II [Gilman and Swiss, *J. Am. Chem. Soc.*, **62**, 1847 (1940)], which differentiates between alkyllithium compounds on the one hand and Grignard reagents and aryllithium compounds on the other. The test is based on the rapid halogen-metal interconversion reaction (see p. 582) between *p*-bromodimethylaniline and alkyllithium compounds. See also color test III [Gilman and Yablunky, *J. Am. Chem. Soc.*, **63**, 839 (1941)] and color test IV [Gilman and Woods, *J. Am. Chem. Soc.* **65**, 33 (1943)].

The progress of the reactions is determined by color test I.[40]

COLOR TEST I. A sample of the reaction mixture (0.5 cc.) is treated with 0.5 cc. of a 1% solution of Michler's ketone in dry benzene and then hydrolyzed by slow addition of 1 cc. of water with shaking. If a green-blue color is noted when a few drops of a 0.2% solution of iodine in acetic acid are added, there is still unchanged lithium reagent present in the solution from which the test sample was taken.

The reactions with organolithium compounds can be effected in the same types of flasks as were used in their preparation. After the completion of the reaction, which usually occurs immediately with vigorous boiling of the ether, the reaction mixture is poured into a separatory funnel containing water and the ether layer is separated. The water solubility of the lithium hydroxide which is formed by the hydrolysis is an advantage over the use of Grignard compounds. The Schlenk tube which is illustrated in the accompanying diagram is suitable for reactions requiring more time. It can be closed by a stopper at the top and a valve at the side arm. If it is necessary to heat the reaction mixture, the components are sealed under nitrogen in an ordinary Schlenk tube and, after the reaction is complete, the tube is opened under nitrogen.



III. INTERCONVERSION REACTIONS WITH ORGANOLITHIUM COMPOUNDS

1. Hydrogen-Metal Interconversion (Metalation)

The alkyl- and aryllithium compounds are, by virtue of their unusual reactivity, suitable for interconversion reactions:

$$RLi + R'H \longrightarrow R'Li + RH$$

When the product is a true organometallic compound, the reaction is termed *metalation.* Grignard compounds either do not give this reaction at all or only under forced conditions. This hydrogen-metal interconversion or metalation can be used for the preparation of lithium derivatives which are difficultly obtainable otherwise and opens up new synthetic possibilities.

Thus, while hydrogen atoms which are bound to oxygen or nitrogen atoms are replaced by the MgX residue of the Grignard reagent (Zerevitinov reaction), hydrogen atoms bound to carbon, except in reactive hydrocarbons such as cyclopentadiene and fluorene, are not replaced by MgX. The organolithium compounds, on the contrary, replace the hydrogen atom on a hydrocarbon in so far as it is activated by a neighboring aryl or vinyl group. The rate of replacement is dependent largely on the nature of the reactants[41] and on the solvent.[42–44]

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[40] Gilman and Schulze, *J. Am. Chem. Soc.*, 47, 2002 (1925).

For example, 9-fluorenyllithium is formed in ether at once and almost quantitatively from fluorene and ethyllithium, while the reaction in benzene requires many hours of heating.[45,46] The resulting fluorenyllithium can be transformed into derivatives such as 9-butylfluorene by means of butyl bromide (in 40% yield) or into 9-acetylfluorene by means of acetyl chloride (in 60% yield).[47]

The metalation of triphenylmethane is more difficult; the reaction mixture with phenyllithium must be heated for several hours at 50° to 60°C. for the preparation of triphenylmethyllithium, while, by way of comparison, the preparation of $(C_6H_5)_3CK$ by means of ethereal phenylisopropylpotassium is complete within a few minutes, as indicated by the following equation[42]:

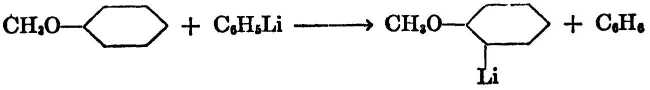
$$(C_6H_5)_3CH + C_6H_5(CH_3)_2CK \longrightarrow (C_6H_5)_3CK + C_6H_5(CH_3)_2CH$$

Since the diphenylvinyl group activates a hydrogen atom more strongly than does the phenyl group, a hydrocarbon such as tetraphenylpentadiene is metalated rapidly by phenyllithium even in the cold:

$$[(C_6H_5)_2C{=}CH]_2CH_2 + C_6H_5Li \longrightarrow [(C_6H_5)_2C{=}CH]_2CHLi + C_6H_6$$

This lithium compound forms deep red solutions from which, on cooling, it separates as crystals with a coppery luster.[18]

In certain aromatic compounds even the hydrogen of a benzene ring is replaceable by lithium by means of organolithium reagents. For example, ethers of phenol and thiophenol[48] can be metalated in the ortho position by the action of butyllithium or phenyllithium. While anisole itself is metalated in a yield of 70% by heating at 100°C. for several hours with phenyllithium[21,22]:



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[41] For *metalation* of hydrogen by the reaction $RLi + H_2 \rightarrow RH + LiH$ see Gilman, Jacoby, and Ludeman, *J. Am. Chem. Soc.*, **60**, 2336 (1938).

[42] Ziegler, *Angew. Chem.*, 49, 455 (1936).

[43] Gilman and Bebb, *J. Am. Chem. Soc.*, **61**, 109 (1939).

[44] Gilman, Jacoby, and Ludeman, *J. Am. Chem. Soc.*, **60**, 2336 (1938).

[45] Ziegler and Jakob, *Ann.*, **511**, 45 (1934).

[46] Schlenk and Bergmann, *Ann.*, **463**, 192 (1928).

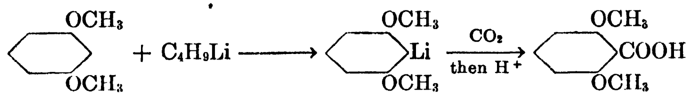
[47] Miller and Bachman, *J. Am. Chem. Soc.*, **57**, 766 (1935).

[48] Thioanisole, however, is metalated laterally by RLi compounds and the carbonation product is (phenylmercapto)acetic acid [Webb, *Iowa State Coll. J. Sci.*, **17**, 152 (1942); *Chem. Abstracts*, **37**, 3413 (1943)].

resorcinol dimethyl ether forms 2,6-dimethoxyphenyllithium in 70% yield even in the cold. Since the metal enters between the two methoxyl groups, the compound formed can be used to synthesize 2-substituted resorcinol derivatives, which are very difficult to obtain otherwise.

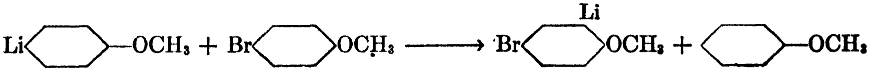
2,6-DIMETHOXYBENZALDEHYDE.[49] A mixture of 13.8 g. of resorcinol dimethyl ether (0.1 mole) and 0.1 mole of phenyllithium in 100 cc. of absolute ether is allowed to stand at room temperature for 60 hours, whereupon the 2-lithio derivative separates in large water-clear crystals. A solution of 13.5 g. of *N*-methylformanilide in 100 cc. of absolute ether is then added dropwise, whereupon the ether starts to boil. After cessation of the reaction, the mixture is allowed to stand for one-half hour and then is poured into an excess of dilute sulfuric acid. The ether layer is separated, dried, and the solvent driven off. The residue is distilled under vacuum at 13 mm. until the distillation temperature reaches 130°C. The solidifying residue yields colorless needles melting at 98° to 99° after crystallization from cyclohexane or from a large quantity of water.[50] Yield, 55%. The semicarbazone formed in the usual manner melts at 189° to 190° after crystallization from chloroform.[50]

This type of reaction has been applied in making 2,6-dimethoxybenzoic acid by the reaction of resorcinol dimethyl ether with *n*-butyllithium followed by carbonation of the lithium derivative with dry ice[51]:



2,3,6-Trimethoxybenzoic acid has been made by the same type of reaction.[52]

The reaction mechanism indicated for the anisole derivative explains why, in the preparation of *p*-anisyllithium from *p*-bromoanisole and lithium (halogen-metal interconversion, p. 582), 5-bromo-2-methoxyphenyllithium[3,21,53] is also formed:



This possibility should be taken into consideration in the syntheses of anisyl compounds.

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[49] Wittig and Faber, unpublished studies. Faber, Dissertation, Freiburg, 1941.

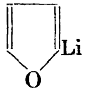
[50] Limaye, *Proc. Indian Acad. Sci.*, A1, 163 (1934); *Chem. Abstracts*, 29, 1796 (1935).

[51] Gilman, Willis, Cook, Webb, and Meals, *J. Am. Chem. Soc.*, 62, 667 (1940).

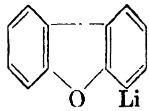
[52] Gilman and Thirtle, *J. Am. Chem. Soc.*, 66, 858 (1944).

[53] Gilman, Langham, and Jacoby, *J. Am. Chem. Soc.*, 61, 106 (1939).

According to Gilman and co-workers[43,54] heterocyclic compounds with O, S, or N as ring members behave as does anisole. By the action of alkyl- or aryllithium the hydrogen atom on the carbon atom nearest to the hetero linkage is replaced by metal. Thus α-furyllithium and 4-dibenzofuryllithium are easily obtained by the reaction of the corresponding heterocycles with phenyllithium:

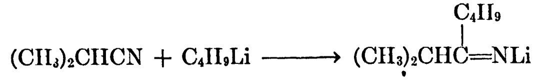


and



The importance of the extremely reactive lithium reagents as intermediates for the introduction of substituents into the aromatic ring is obvious.

An impressive example of the versatility of organolithium compounds for synthetic work is the reaction of organometallic compounds with nitriles.[55] Under favorable conditions tertiary nitriles are produced. Butyllithium, unlike the organosodium compounds, does not metalate isobutyronitrile but adds to the nitrile group even though the hydrogen atom is activated:



$$(CH_3)_2CHCN + C_4H_9Li \longrightarrow (CH_3)_2CH\overset{C_4H_9}{\overset{|}{C}}{=}NLi$$

If, however, the alkyllithium is allowed to react first on diethylamine, lithium diethylamide is formed, which then metalates the nitrile:

$$(CH_3)_2CHCN + LiN(C_2H_5)_2 \longrightarrow (CH_3)_2C(Li)CN + HN(C_2H_5)_2$$

The lithium compound which is formed can be converted into a tertiary nitrile by reaction with an alkyl halide, for example with allyl chloride into dimethylallylacetonitrile.

Dimethylallylacetonitrile. In a three-necked flask is placed 0.3 mole of phenyllithium as an approximately 1 *N* solution in ether. A dry nitrogen atomosphere is maintained. While being stirred and cooled in a freezing mixture, the solution is treated dropwise with 21.9 g. (0.3 mole) of dry diethylamine. A thermometer in the liquid shows a temperature rise of several degrees. Apparently no change occurs in the solution, but color test I[40] is negative. Next 20.7 g. (0.3 mole) of isobutyronitrile is dropped in and stirring is continued for a few minutes longer. The solution of lithium isobutyronitrile is stable under nitrogen; the color

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[54] Gilman and Young, *J. Am. Chem. Soc.*, **56**, 1415 (1934); **57**, 1121 (1935). Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1939). Gilman and Stuckwisch, *J. Am. Chem. Soc.*, **67**, 877 (1945).

[55] Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932).

test is positive again. For alkylation, 22.8 g. (0.3 mole) of allyl chloride is finally added dropwise. The reaction occurs spontaneously even below 0°C., and the solution becomes turbid (LiCl). Finally the reaction mixture is refluxed for a short time and worked up. The yield of dimethylallylacetonitrile boiling at 150° is 27 g. (82.5%).

The work of Ziegler and co-workers[56] with lithium dialkylamide as a condensation agent for the synthesis of macrocyclic rings from dinitriles should be mentioned.

In this connection the use of organolithium compounds for syntheses which start with hydrazobenzene should be reported.[17,57] The dilithium adduct of azobenzene (I), whose formation in ether from azobenzene and metallic lithium (through the monolithium adduct II as intermediate) requires months, is easily obtained by the reaction of methyllithium on hydrazobenzene. The addition reaction with azobenzene leads to the well crystallized radical II:

$$\underset{(I)}{C_6H_5N(Li)N(Li)C_6H_5} + C_6H_5N{=}NC_6H_5 \longrightarrow \underset{(II)}{2C_6H_5N(Li)NC_6H_5}\ \vdots$$

To a solution of 7.4 g. (0.04 mole) of hydrazobenzene in 80 cc. of absolute ether under nitrogen is added dropwise an ethereal solution of 0.08 mole of methyllithium. Methane is evolved vigorously. The monolithiohydrazobenzene separates in colorless temporary crystals and again dissolves with formation of the *N*,*N*′-dilithiohydrazobenzene (I).

If 0.04 mole of azobenzene in a little ether is added to this solution, the desired nitrogen radical (II), which crystallizes out in dark brown needles, is formed at once.

N,*N*′-DIMETHYLHYDRAZOBENZENE. Dimethyl sulfate (0.1 mole) in absolute ether is added dropwise during 30 minutes to the solution of *N*,*N*′-dilithiohydrazobenzene which is cooled with ice water. After standing for 15 hours, the reaction mixture is shaken with ammonium hydroxide to destroy the excess dimethyl sulfate. Distillation of the ether leaves 7.7 g. of *N*,*N*′-dimethylhydrazobenzene with a melting point of 28° to 30°C. After crystallization from petroleum ether the compound melts at 33° to 33.5°.[58]

Analysis—$C_{14}H_{16}N_2$. Calculated: N, 13.2; found: N, 13.5.

N,*N*′-DIPHENYLPYRAZOLIDINE. For this preparation the solution of 0.04 mole of *N*,*N*′-dilithiohydrazobenzene is treated with 0.044 mole of

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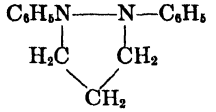
[56] Ziegler, Eberle, and Ohlinger, *Ann.*, **504**, 94 (1933). Ziegler and Weber, *Ann.*, **512**, 164 (1934).

[57] Wittig, Pockels, and Knackstedt, unpublished studies.

[58] Wieland and Fressel obtained the material as an impure oil [*Ann.*, **392**, 147 (1912)].



trimethylene bromide. After standing for 1 day, the reaction mixture is shaken with water, the ether distilled off, and the residue agitated with petroleum ether to remove the azobenzene formed. On crystallization from alcohol (charcoal) the pyrazolidine is obtained in a yield of 3.6 g. and melts at 98° to 98.5°C.

Analysis—$C_{15}H_{16}N_2$. Calculated: N, 12.5; found: N, 12.6.

2. Metal-Metal Interconversion

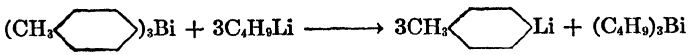
Metalation by organolithium compounds is possible if the hydrogen atom has been made sufficiently labile. Interconversion is facilitated still further if a metal substituent is to be replaced instead of a hydrogen atom.

By such a metal-metal interconversion reaction Ziegler and Dersch[9]

$$C_6H_5CH_2MgCl + 2C_6H_5Li \longrightarrow C_6H_5CH_2Li + (C_6H_5)_2Mg + LiCl$$

succeeded in obtaining benzyllithium, which is difficultly accessible otherwise. This compound, which forms rapidly in ether, is usable for further reactions if the diphenylmagnesium formed simultaneously does not interfere.

This type of interconversion reaction makes possible the synthesis of other organometallic compounds from lithium derivatives. Thus, butyllithium reacts with tritolylbismuth with the formation of tolyllithium and tributylbismuth[9,59]:



Other organometallic compounds are formed in yields up to 90% by the reaction of metal halides with organolithium compounds:

$$MCl_x + xRLi \longrightarrow R_xM + xLiCl$$

Halides of cadmium,[60] thallium,[61] tin,[62] and lead[62] exhibit this reaction

3. Halogen-Metal Interconversion

Recently Gilman[53,63,64] and Wittig[21] found that the lithium atom of the

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[59] Gilman, Yablunky, and Svigoon, *J. Am. Chem. Soc.*, **61**, 1170 (1939).

[60] Nesmeyanov and Makarova, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 2649 (1937); *Chem. Abstracts*, **32**, 2095 (1938).

[61] Birch, *J. Chem. Soc.*, **1934**, 1132.

[62] Austin, *J. Am. Chem. Soc.*, **54**, 3726 (1932). Mel'nikov and Gracheva, *J. Gen. Chem.* (*U. S. S. R.*), **6**, 634 (1936); *Chem. Abstracts*, **30**, 5557 (1936).

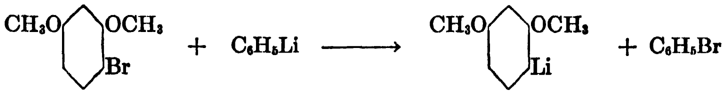
[63] Gilman, Willis, and Swislowsky, *J. Am. Chem. Soc.*, **61**, 1371 (1939).

[64] Gilman and Woods, *J. Am. Chem. Soc.*, **66**, 1981 (1944).

alkyl- or aryllithium compound may be replaced by halogen as well as by hydrogen or other metallic substituents:[39,65]

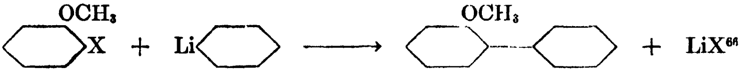
$$RX + R'Li \longrightarrow RLi + R'X$$

If, for example, an ethereal solution of 4-bromoresorcinol dimethyl ether is treated with the equivalent quantity of phenyllithium, 4-lithioresorcinol dimethyl ether and bromobenzene are formed immediately and almost quantitatively[22]:



Thus, the isomer of the 2-lithio derivative (page 579) can be obtained. These isomers react with benzophenone, yielding 2,4- or 2,6-dimethoxyphenyldiphenylcarbinol.

Similarly, *o*-iodoanisole reacts at once in the cold with phenyllithium, yielding *o*-anisyllithium and iodobenzene; the same reaction between *o*-bromoanisole and phenyllithium requires about 1 hour.[66] However, in the reaction of *o*-chloro- and *o*-fluoroanisole with the same lithium reagent, the following side reaction occurs to some extent:



Obviously, interconversion reactions dominate when the halogen atom, because of increasing polarizability and polarization, approaches the cationic state.[67]

4. Coupling Reactions

That halogen bound to an aliphatic group is also replaceable by lithium is shown by the behavior of benzyl bromide (not benzyl chloride, which reacts entirely differently) toward phenyllithium.[23,68] Here the following reactions take place:

$$C_6H_5CH_2Br + C_6H_5Li \longrightarrow C_6H_5CH_2Li + C_6H_5Br \qquad (1)$$

$$C_6H_5CH_2Br + C_6H_5CH_2Li \longrightarrow LiBr + C_6H_5CH_2CH_2C_6H_5 \qquad (2)$$

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[65] The halogen-metal interconversion reaction is an excellent method for organolithium compounds in which reaction of the metal with the aryl compound fails. For example, *m*-bromobenzotrifluoride does not react with lithium but gives an excellent yield of the lithium compounds when treated with *n*-butyllithium (see foot-note 64).

[66] Wittig and Fuhrmann, *Ber.*, **73**, 1197 (1940).

[67] According to personal observation (Wittig) an iodine atom may be introduced into the organic residue of the organolithium compound by reaction with I_2: $C_6H_5Li + I_2 \rightarrow C_6H_5I + LiI$. (See also foot-note 52.) The significance of the polarization of the halogen in this type of reaction is discussed by Meerwein, Hofmann, and Schill, *J. prakt. Chem.*, **154**, 266 (1940).

[68] G. Wittig and H. Witt, *Ber.*, **74**, 1474 (1941).

Bibenzyl and bromobenzene are obtained in yields which correspond to these equations; the intermediate benzyllithium, on the other hand, cannot be isolated, since it reacts at once with the benzyl bromide still present according to Reaction 2.

Bibenzyl. To a solution of 20 g. (0.12 mole) of benzyl bromide in 90 cc. of ether under nitrogen is added dropwise an ethereal solution of 0.12 mole of phenyllithium with stirring or shaking, whereupon the ether starts to boil. After some time the brown solution is poured into water and the ethereal layer separated. The titration of the aqueous solution gave a composition of 49.5% LiOH and 50.5% LiBr. After the ether solution was dried over sodium sulfate and the solvent distilled, the residue was fractionated at 11 mm. pressure, giving 6.3 g. of bromobenzene at 40° to 46°C. and 9.7 g. of bibenzyl at 132° to 134°. The bibenzyl solidified and gave no melting point depression with an authentic sample, m.p. 53.5° to 54.5°C.

In most cases of reaction of a halogen compound with a lithium derivative, the normal process occurs spontaneously, that is the formation of lithium halide with coupling of the two organic residues.[69] This reaction becomes of preparative significance if it is desired to couple two different residues, a task which is carried out only with considerable losses by the Wurtz-Fittig synthesis. In the reaction of the lithium compounds with halogenated hydrocarbons, the iodine derivatives are most suitable, since, in general, they react most rapidly. The graduated behavior of the alkyl halides is illustrated in the following example whereby octane is formed by the reaction of *n*-butyllithium and *n*-butyl halides in 0.5 *N* solution[11,70,71] in the indicated reaction times.[72]

n-Butyl	In benzene (half life)	In ether
Iodide	3 hrs.	Immediate reaction
Bromide	3–4 days	Reaction complete in 5 hrs.
Chloride	No noticeable reaction in 2 days	Half life 40 hrs.

IV. ADDITION REACTIONS OF ORGANOLITHIUM COMPOUNDS

The addition of organolithium compounds to unsaturated molecules is another example of their exceptional reactivity. In the majority of cases immediate and complete reaction is obtained. This high reactivity is especially valuable in effecting addition reactions which fail to occur with magnesium compounds.

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[69] Aryl-aryl coupling products generally form with some difficulty. Addition of catalytic quantities of metal halides, however, gives high yields of coupling products; see among others Kharasch and Reynolds, *J. Am. Chem. Soc.*, **63**, 3239 (1941).

[70] Ziegler, Crössman, Kleiner, and Schäfer, *Ann.*, **473**, 1 (1929).

[71] Ziegler, Dersch, and Wollthan, *Ann.*, **511**, 13 (1934).

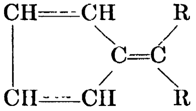
[72] The dependence of the speed of the reaction on the R residue of RLi has been studied by Ziegler and co-workers (foot-notes 70 and 71); see also Gilman and Kirby (foot-note 1).

1. Addition to C=C

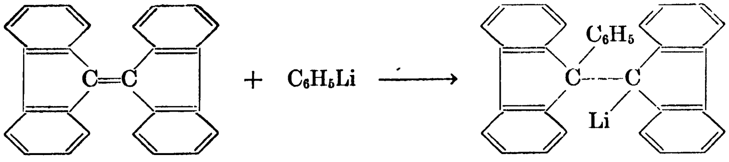
Lithium compounds, unlike the magnesium derivatives, can be added to unsaturated aliphatic hydrocarbons which contain two conjugated double bonds, to certain phenylated ethylenes, and to aromatic hydrocarbons such as anthracene. For example, butyllithium adds to 1,1-diphenylethylene[70] according to the equation:

$$(C_6H_5)_2C{=}CH_2 + C_4H_9Li \longrightarrow (C_6H_5)_2C(Li)CH_2C_4H_9$$

In this case, as with interconversion reactions, the rate of reaction is dependent on the solvent; ether accelerates the addition, while benzene retards it. The fulvenes,



whose semicyclic double bond takes on the activity of a C=O bond because of the bifurcated conjugation, are especially suited to reaction. According to Ziegler and Schäfer,[73] dimethylfulvene reacts with phenyllithium with vigorous refluxing of the ether; $\Delta^{9,9'}$-bifluorene also adds phenyllithium quickly and smoothly to the reactive double bond:



The study of these addition reactions led Ziegler and co-workers[34,71,74] to the conclusion that the polymerization of butadiene by alkali metals and organoalkali compounds is an organometallic synthesis.[75] If butadiene is passed into an ethereal solution of butyllithium, the gas is absorbed with vigorous heat evolution and the solution, originally colorless, becomes yellow by formation of the adduct:

$$C_4H_9CH_2CH{=}CHCH_2Li \quad \text{or} \quad C_4H_9CH_2CH(Li)CH{=}CH_2$$

These lithium adducts may, in turn, add to butadiene in the 1,4 or 1,2 positions stepwise to form lithium adducts of the general composition C_4H_9-

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[73] Ziegler and Schäfer, *Ann.*, **511**, 101 (1934).

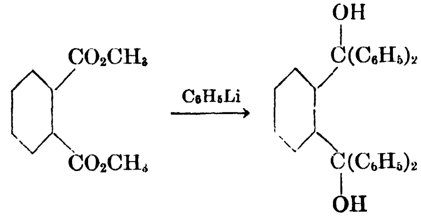
[74] Ziegler, Wollthan, and Wenz, *Ann.*, **511**, 64 (1934). Ziegler, Grimm, and Willer, *ibid.*, **542**, 90 (1939).

[75] Ziegler, *Angew. Chem.*, **49**, 499 (1936).

$(C_4H_6)_nLi$. The composition and properties of the final high molecular products depend on the length of reaction time and the temperature.

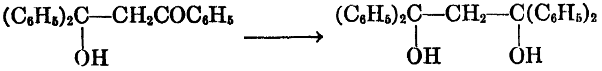
2. Addition to C=O

In addition reactions involving compounds containing carbonyl groups the analogies between organolithium and organomagnesium compounds are especially evident. Therefore in reactions with aldehydes, ketones, and esters the more readily available Grignard reagents are generally used. However, certain diketones and dicarboxylic esters[76] yield glycols, which are important for the preparation of radicals, either in poor yield or not at all with magnesium compounds. Organolithium compounds, on the other hand, give excellent yields of the glycols. Thus the reaction of *o*-dimethyl phthalate fails with phenylmagnesium bromide but goes smoothly with phenyllithium[12]:



o-BIS(DIPHENYLHYDROXYMETHYL)BENZENE. To a solution of 1.9 g. (0.01 mole) of *o*-dimethyl phthalate in 10 cc. of ether under nitrogen is added dropwise an ether solution of 0.04 mole of phenyllithium. The reaction, which occurs with vigorous refluxing, is ended with the last drop of phenyllithium solution. The reaction mixture is poured into water and the *o*-bis(diphenylhydroxymethyl)benzene, m.p. 203.5°C., is obtained in 90% yield after crystallization from benzene-petroleum ether.

Another example is the synthesis of tetraphenylpropanediol (IV),[15] which cannot be prepared by the reaction of phenylmagnesium bromide on malonic ester, since the reaction stops with the formation of the ketone (III):



$$\underset{\text{(III)}}{(C_6H_5)_2\underset{|\atop OH}{C}{-}CH_2COC_6H_5} \longrightarrow \underset{\text{(IV)}}{(C_6H_5)_2\underset{|\atop OH}{C}{-}CH_2{-}\underset{|\atop OH}{C}(C_6H_5)_2}$$

Under energetic conditions III dissociates into benzophenone and acetophenone which then react further with the phenylmagnesium bromide to form triphenylcarbinol and diphenylmethylcarbinol; the same reactions are observed with phenyllithium at 15° to 20°C. On the other hand, because of the reactivity of the lithium compound, the reaction (III) → (IV) can be effected at −80° and the desired glycol (IV) is obtained in 70% yield.

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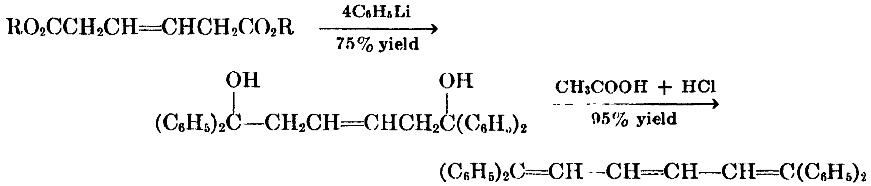
[76] For the reactions of tricarboxylic esters with phenyllithium see Wittig and Kosack (foot-note 25) and Leo, *Ber.*, **70**, 1691 (1937).

The smooth reaction of unsaturated dicarboxylic esters of the composition $RO_2CCH_2(CH{=}CH)_nCH_2CO_2R$ with phenyllithium makes possible the preparation of ω,ω′-tetraphenyl polyenes,[19] such as tetraphenylhexatriene:

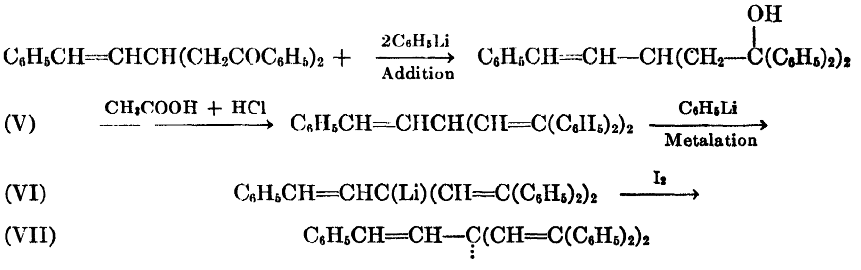


$$RO_2CCH_2CH{=}CHCH_2CO_2R \xrightarrow[75\%\ \text{yield}]{4C_6H_5Li}$$

$$(C_6H_5)_2\overset{OH}{\overset{|}{C}}-CH_2CH{=}CHCH_2\overset{OH}{\overset{|}{C}}(C_6H_5)_2 \xrightarrow[95\%\ \text{yield}]{CH_3COOH\ +\ HCl}$$

$$(C_6H_5)_2C{=}CH-CH{=}CH-CH{=}C(C_6H_5)_2$$

The synthesis of styryl di(β,β-diphenylvinyl)methyl[25] is interesting in that it involves a bifunctional use of organolithium compounds:



$$C_6H_5CH{=}CHCH(CH_2COC_6H_5)_2 + \xrightarrow[\text{Addition}]{2C_6H_5Li} C_6H_5CH{=}CH-CH(CH_2-\overset{OH}{\overset{|}{C}}(C_6H_5)_2)_2$$

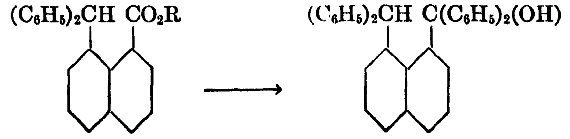
$$\text{(V)} \quad \xrightarrow{CH_3COOH\ +\ HCl} C_6H_5CH{=}CHCH(CH{=}C(C_6H_5)_2)_2 \xrightarrow[\text{Metalation}]{C_6H_5Li}$$

$$\text{(VI)} \quad C_6H_5CH{=}CHC(Li)(CH{=}C(C_6H_5)_2)_2 \xrightarrow{I_2}$$

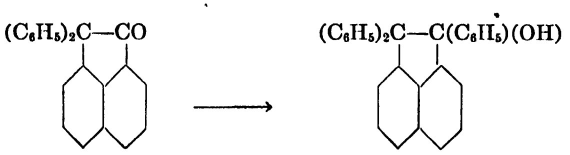
$$\text{(VII)} \quad C_6H_5CH{=}CH-\underset{\vdots}{C}(CH{=}C(C_6H_5)_2)_2$$

The first function is addition to the carbonyl group; the second is metalation of the hydrocarbon V. The lithium derivative (VI) precipitates in crystals with a green metallic luster and the solution takes on a deep violet color. The metal elimination by iodine leads to the desired radical (VII). Formulas VI and VII are to be considered in equilibrium with their allyl tautomers.

The superiority of the organolithium compounds is especially noted in the case of those carbonyl derivatives which do not react with magnesium compounds because of steric hindrance. To this group belong the following two naphthalene derivatives which yield the corresponding carbinols with phenyllithium rapidly and in good yields.[16]



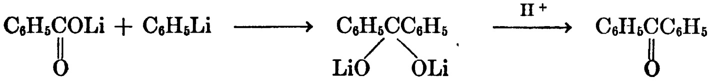
(1)



(2)

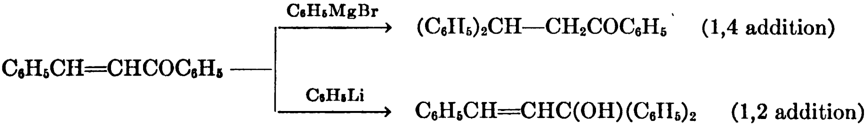
On the basis of the investigations made so far, it can be said that phenyllithium is the most sensitive reagent available for the C=O group.[77]

The differences in the reactions of organolithium and organomagnesium compounds with carbon dioxide[78] are really noteworthy. While Grignard compounds give good yields of carboxylic acids with solid carbon dioxide the increased reactivity of the lithium derivatives causes the addition, to some extent, of a second molecule of organolithium compound to the lithium salt of the acid. For example, phenyllithium adds to the lithium benzoate arising from the reaction of phenyllithium with carbon dioxide.[79] The product, dilithium diphenylmethanediol, reacts no further and forms benzophenone by hydrolysis. Despite this side reaction the yield of benzoic acid is about 60%.



$$C_6H_5\underset{\displaystyle O}{\overset{}{C}}OLi + C_6H_5Li \longrightarrow C_6H_5C(OLi)_2C_6H_5 \xrightarrow{H^+} C_6H_5\underset{\displaystyle O}{C}C_6H_5$$

A contrasting behavior is observed also in the reaction of Li and Mg compounds with α,β-unsaturated ketones. Thus, benzalacetophenone gives diphenylpropiophenone with phenylmagnesium bromide. On the other hand, diphenylstyrylcarbinol is formed in the reaction with phenyllithium[80]:



$$C_6H_5CH{=}CHCOC_6H_5 \xrightarrow{C_6H_5MgBr} (C_6H_5)_2CH{-}CH_2COC_6H_5 \quad \text{(1,4 addition)}$$

$$C_6H_5CH{=}CHCOC_6H_5 \xrightarrow{C_6H_5Li} C_6H_5CH{=}CHC(OH)(C_6H_5)_2 \quad \text{(1,2 addition)}$$

The corresponding beryllium derivatives behave like the organomagnesium compounds, while phenylcalcium iodide in this case reacts like phenyllithium.[81]

The behavior of the magnesium and lithium compounds toward 1,8-

---

[77] Personal experimentation has shown that carbon monoxide itself reacts with phenyllithium in the cold and yields, in addition to biphenyl and other compounds, α,α-diphenylacetophenone, $(C_6H_5)_2CHCOC_6H_5$, while it reacts with phenylmagnesium bromide at 75°C. in an autoclave to give benzoin [Fischer and Stoffers, *Ann.*, **500**, 253 (1933)].

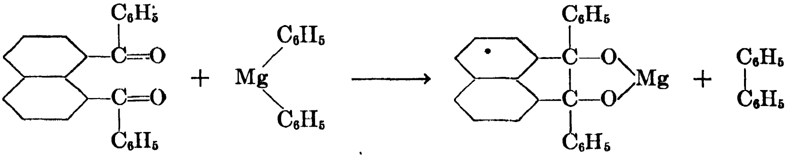
[78] With CS_2, organolithium and organomagnesium compounds form dithiocarboxylates [Schönberg, Stephenson, Kaltschmitt, Petersen, and Schulten, *Ber.*, **66**, 237 (1933)].

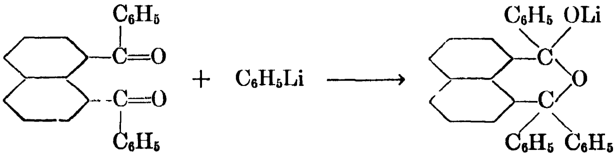
[79] Gilman and Van Ess, *J. Am. Chem. Soc.*, **55**, 1258 (1933).

[80] Lüttringhaus, Jr., *Ber.*, **67**, 1602 (1934). Koelsch and Rosewald, *J. Am. Chem. Soc.*, **59**, 2166 (1937).

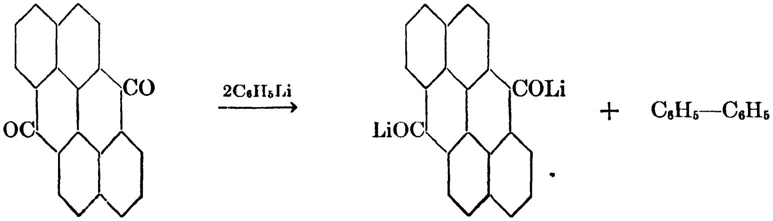
[81] Gilman, *Organic Chemistry*, 2nd ed., Wiley, New York, 1943, p. 526.

dibenzoylnaphthalene[13] differs in another way. While phenylmagnesium bromide or diphenylmagnesium reduces the ketone, phenyllithium adds to the carbonyl group normally in accord with the greater polarity of the

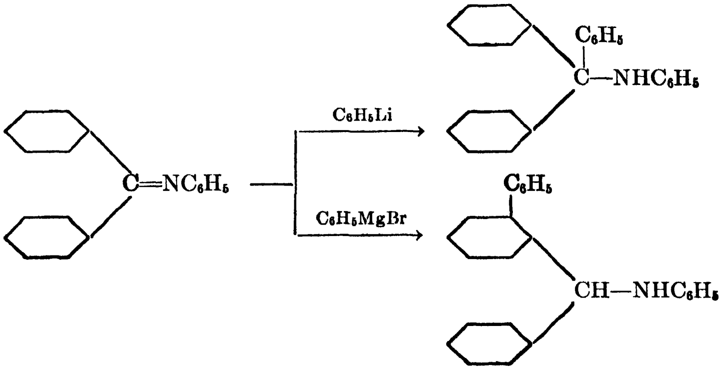




C—Li bond.[82] In its reaction with anthanthrone,[83] however, phenyllithium acts as a reducing agent.

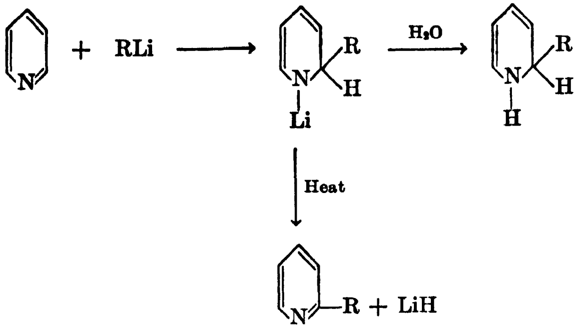


Other fundamental differences are observed in the addition of phenyllithium and phenylmagnesium bromide to benzophenoneanil, which, like benzalacetophenone adds the lithium compound in the 1,2 position and the Grignard reagent in the 1,4 position[1,84]:



3. Addition to C=N

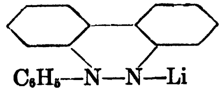
Besides these types of contrasting reaction courses, the increased suitability of lithium derivatives for addition in the series of C=N compounds offers many advantages over the use of the magnesium compounds. Thus, Ziegler and Zeiser[85] found that pyridine, quinoline, isoquinoline, and acridone add alkyl- and aryllithium compounds at room temperature with vigorous reaction. By subsequent hydrolysis, substituted dihydro compounds are obtained which on treatment with nitrobenzene or other dehydrogenating agents are transformed into the alkylated or arylated pyridine derivatives. This end can also be reached directly if the original lithium adduct is heated for some time in the solution, whereupon lithium hydride splits out (Tschitschibabin reaction). It is obvious that these reactions are important for the synthesis of alkylated and arylated heterocycles. They have been applied lately in antimalarial research.[64,86]



α-*n*-Butylpyridine from Pyridine. To pure dry pyridine under nitrogen is added an equimolecular portion of *n*-butyllithium in benzene

---

[82] The enhanced additivity of lithium compounds on one hand and the reducing behavior of magnesium derivatives on the other are evidenced in their reactions with azobenzene [Gilman and Bailie, *J. Org. Chem.*, 2, 84 (1937)] and benzo[*c*]cinnoline (see foot-note 17). From personal observation, phenyllithium adds to azobenzene, forming triphenylhydrazine, but acts partly as a reducing agent to give hydrazobenzene; benzo[*c*]cinnoline, on the other hand, adds phenyllithium smoothly to the azo group, forming the derivative:



[83] Petri, Dissertation, Marburg, 1935, p. 15.

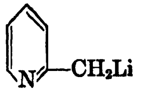
[84] Gilman and Breuer, *J. Am. Chem. Soc.*, 55, 1262 (1933).

[85] Ziegler and Zeiser, *Ber.*, 63, 1847 (1930); *Ann.*, 485, 174 (1931). Walters and McElvain, *J. Am. Chem. Soc.*, 55, 4625 (1933). Haskelberg, *Chem. and Ind.*, 54, 261 (1935).

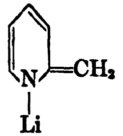
[86] Gilman and Blume, *J. Am. Chem. Soc.*, 65, 2467 (1943). Gilman and Spatz, *ibid.*, 66, 621 (1944). Gilman, Stuckwisch, and Nobis, *ibid.*, 68, 326 (1946).

(larger quantities slowly and with cooling) and the mixture is heated in a sealed tube for 3 hours at 90° to 100°C. The originally dirty orange colored contents become somewhat darker and lithium hydride separates as a colorless fine powdery deposit. After the mixture is cooled, water is added and hydrogen is evolved vigorously. The benzene solution of the *α-n*-butylpyridine is washed with water and extracted with hydrochloric acid. The base is recovered from the acid in the customary manner. The boiling point of the colorless product is 191° to 193°C.

Alkyl- and aryllithium compounds react with *α*-alkylpyridine and *α*-alkylquinoline, etc., replacing the reactive hydrogen by lithium:



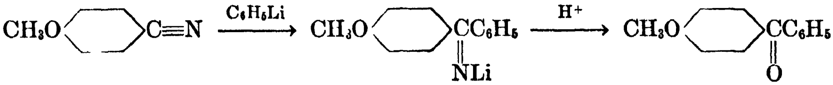
or



Further syntheses were made possible by these compounds. For example, the side chain may be lengthened by reaction with alkyl halides. Thus, Bergmann and Rosenthal[87] made the compounds illustrated above from phenyllithium and *α*-picoline and synthesized coniine by treatment with ethyl bromide and subsequent reduction of the *α*-propylpyridine with sodium and alcohol.

4. Addition to C≡N

Gilman and Kirby[1] found that methyl- and phenyllithium react readily with nitriles to give isolatable products, but little further work of a preparative character has been done on this reaction. For example, *p*-methoxybenzonitrile reacts with phenyllithium within 30 minutes to give, after hydrolysis, a yield of *p*-methoxybenzophenone amounting to 85%:



In the relatively few years since Ziegler and Colonius[11] made organolithium compounds easily accessible a wealth of information has been accumulated. The chemistry of organolithium compounds has undergone a development which, in its preparative significance and theoretical implications, is still in progress. On the basis of their enhanced reactivity, as well as ether solubility and stability, lithium derivatives have become a valuable aid in synthetic organic chemistry.

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[87] Bergmann and Rosenthal, *J. prakt. Chem.*, **135**, 267 (1932).

ADDENDUM

to W. Bockemüller, "Organic Fluorine Compounds"

(*pages 229–248*)

By CHARLES J. KIBLER

Since the translation of this chapter was completed, a considerable number of papers dealing with the preparation and uses of fluorine, hydrogen fluoride, and organic fluorine compounds has been published. By far the greatest part of the work resulted from research initiated by the Office of Scientific Research and Development and later sponsored by the Manhattan District, United States Army Corps of Engineers. Much of it was published as a group of papers in the March, 1947, issue of *Industrial and Engineering Chemistry*.[1] Moreover, there has appeared an excellent review paper by Bigelow.[2]

A considerable amount of work has been done on the preparation of *fluorohydrocarbons*, *chlorofluorocarbons*, and *fluorocarbons*.[3–9] These compounds have found use as extremely stable lubricating oils and greases[3,5] and are useful in the separation of uranium isotopes.[6] *Fluorocarbons* are prepared by the catalytic fluorination of hydrocarbons employing AgF_2 as catalyst,[3] by the reaction of CoF_3 with vaporized hydrocarbons or fluorohydrocarbons at elevated temperatures,[10] and by the action of CoF_3 on chlorinated hydrocarbons.[6] Fluorinated *heterocyclic compounds*[11] have also been prepared. Trifluoromethylpyridine and trifluoromethyltriazines apparently form from the trichloromethyl derivatives as readily as does trifluoromethylbenzene from trichloromethylbenzene. These compounds show promise as heat transfer agents.

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[1] *Ind. Eng. Chem.*, **39**, 235–434 (1947); *Ind. Eng. Chem., Anal. Ed.*, **19**, 146–157, 193–196 (1947). One of these papers deals with the nomenclature of organofluorides; eleven papers treat the generation, handling and disposal of fluorine; fourteen papers deal with the industrial scale development of fluorocarbon processes; twenty-one papers discuss the chemistry of fluorine and fluorine compounds; and six papers deal with the analysis of fluorine or fluorine-containing compounds.

[2] Bigelow, *Chem. Revs.*, **40**, 51–116 (1947).

[3] Cady, Grosse, Barber, Burger, and Sheldon, *Ind. Eng. Chem.*, **39**, 290 (1947).

[4] Couper, Downing, Lulek, Perkins, Stilmar, and Struve, *ibid.*, **39**, 346 (1947).

[5] Grosse and Cady, *ibid.*, **39**, 367 (1947).

[6] McBee *et al.*, *ibid.*, **39**, 298 (1947).

[7] Fowler, Hamilton, Kasper, Weber, Burford, and Anderson, *ibid.*, **39**, 375 (1947).

[8] McBee, Lindgreen, and Ligett, *ibid.*, **39**, 379 (1947).

[9] McBee and Bechtol, *ibid.*, **39**, 380 (1947).

[10] Fowler, Burford, Hamilton, Sweet, Weber, Kasper, and Litant, *ibid.*, **39**, 292 (1947); Benner, Benning, Downing, Irwin, Johnson, Linch, Parmelee, and Wirth, *ibid.*, **39**, 329 (1947).

[11] McBee, Hass, and Hodnett, *ibid.*, **39**, 389 (1947). McBee, Pierce, and Bolt, *ibid.*, **39**, 391 (1947). Ponterman and Girardet, *Helv. Chim. Acta*, **30**, 107 (1947).

Unsaturated fluorocarbons such as tetrafluoroethylene[12] have been *polymerized*[13,14] to form plastics of considerable interest because of their thermal stability and chemical inertness. The plastic, Teflon,[13] made by polymerization of tetrafluoroethylene, has been particularly useful in the generation and handling of fluorine.[15] Highly stable chlorofluorocarbon polymer oils, greases, and waxes[16] have been prepared from chlorotrifluoroethylene. Polymers in the desired range of molecular weight were prepared by solution polymerization with peroxide promotion. After polymerization, the products were treated with CoF_3 to fluorinate reactive end groupings introduced during the reaction.

A method has been patented for the preparation of vinyl fluorides by the addition of hydrogen fluoride to acetylenic compounds in the presence of mercury nitrates at 20–100°C.[17] Methyl difluoroacetate, *n*-fluorohexane, and similar compounds are conveniently prepared by the action of anhydrous KF on the corresponding chloro derivatives in a steel autoclave at 200–250°C.[18]

A new synthesis of *trifluoroacetic acid* has recently been announced.[19] Hexachlorobutadiene, available commercially, is converted to trifluoroacetic acid according to the following scheme in an over-all yield of 83%:

$$CCl_2{=}CClCCl{=}CCl_2 + Cl_2 \longrightarrow CCl_3CCl{=}CClCCl_3$$

$$CCl_3CCl{=}CClCCl_3 \xrightarrow{SbF_3Cl_2} CF_3CCl{=}CClCF_3$$

$$CF_3CCl{=}CClCF_3 \xrightarrow{KMnO_4} 2\ CF_3CO_2H$$

Henne and co-workers[20] have condensed ethyl trifluoroacetate with ethyl acetate, acetone, and trifluoroacetone preparing the β-ketoester or β-diketones in good yields.

Numerous chlorofluoro *derivatives of propane*[21] have been prepared for the purpose of studying their physiological activity. An attempt has been made to prepare a series of fluorinated *aliphatic acids*[22] in which the

[12] Benning, Downing, and Plunkett, U. S. Patent 2,401,897 (1946); *Chem. Abstracts*, 40, 5066 (1946).

[13] Brubaker, U. S. Patent 2,393,967 (1946).

[14] Hanford and Joyce, *J. Am. Chem. Soc.*, 68, 2082 (1946).

[15] Renfrew and Lewis, *Ind. Eng. Chem.*, 38, 870 (1946). McBee, *ibid.*, 39, 237 (1947).

[16] Miller, Dittman, Ehrenfeld, and Prober, *ibid.*, 39, 333 (1947).

[17] E. I. du Pont de Nemours & Co., British Patent 580,910 (1946).

[18] Gryszkiewicz-Trochimowski *et al.*, *Rec. trav. chim.*, 66, 416 (1947).

[19] Henne and Trott, *J. Am. Chem. Soc.*, 69, 1820 (1947).

[20] Henne, Newman, Quill, and Staniforth, *ibid.*, 69, 1819 (1947).

[21] McBee, Hass, Thomas, Toland, and Truchan, *ibid.*, 69, 944 (1947).

[22] Henne and Zimmerschied, *ibid.*, 69, 281 (1947).

fluorine atoms are progressively further removed from the carboxyl group to study the effect of fluorine substitution on the strength of the acids.

Trifluoromethylphenyl ethers[23] may be prepared by heating the appropriate trifluoromethylchlorobenzene with sodium alcoholate. The reaction proceeds most readily when the trifluoromethyl group is ortho or para to the chlorine. The fluorine atoms are apparently unaffected by the sodium alcoholate. However, Jones[24] has shown that the fluorine atoms of a trifluoromethyl group are readily hydrolyzed if the trifluoromethyl group is ortho or para to an amino or hydroxyl group.

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[23] McBee, Bolt, Graham, and Tebbe, *J. Am. Chem. Soc.*, 69, 947 (1947).
[24] Jones, *ibid.*, 69, 2347 (1947).

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